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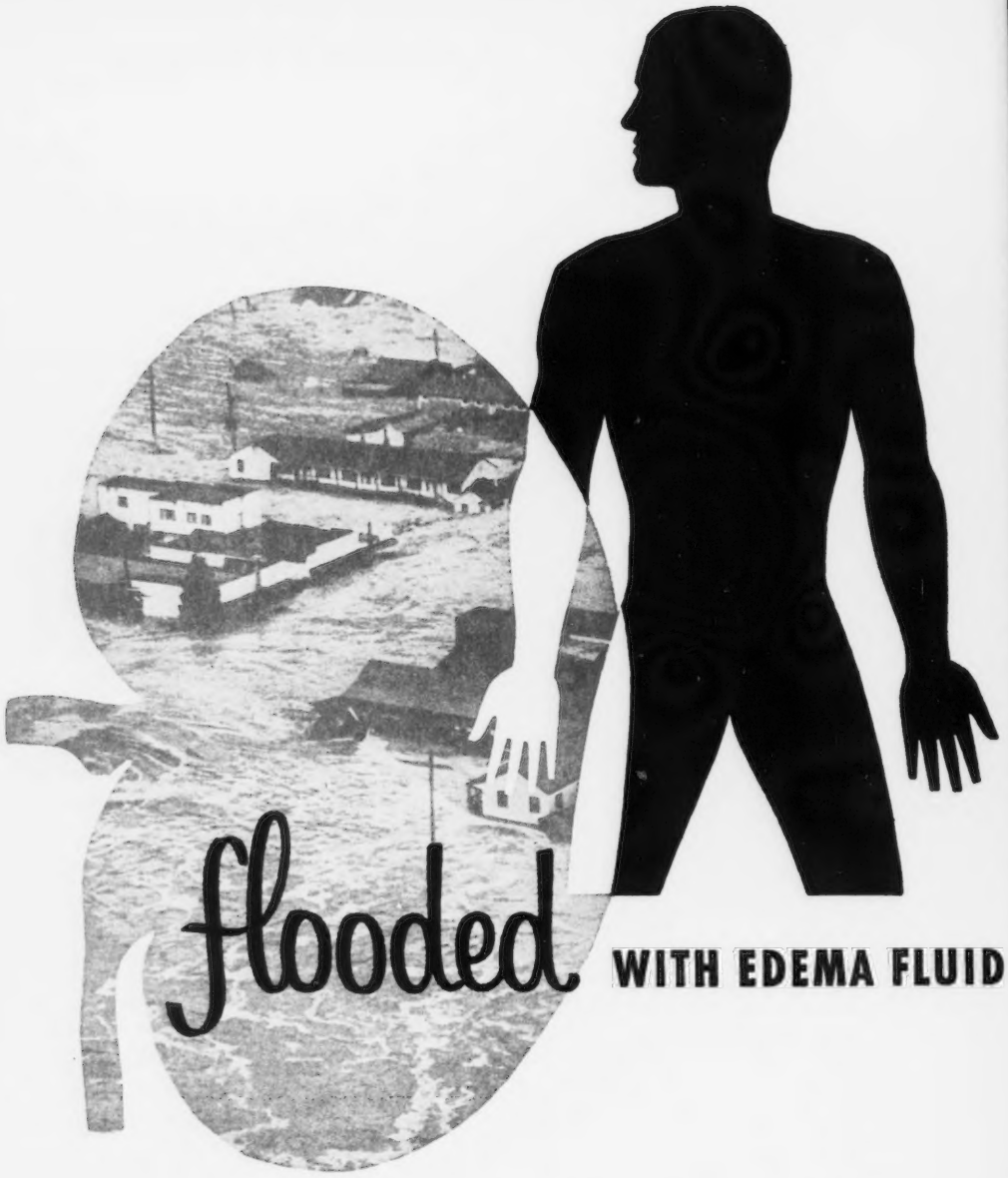

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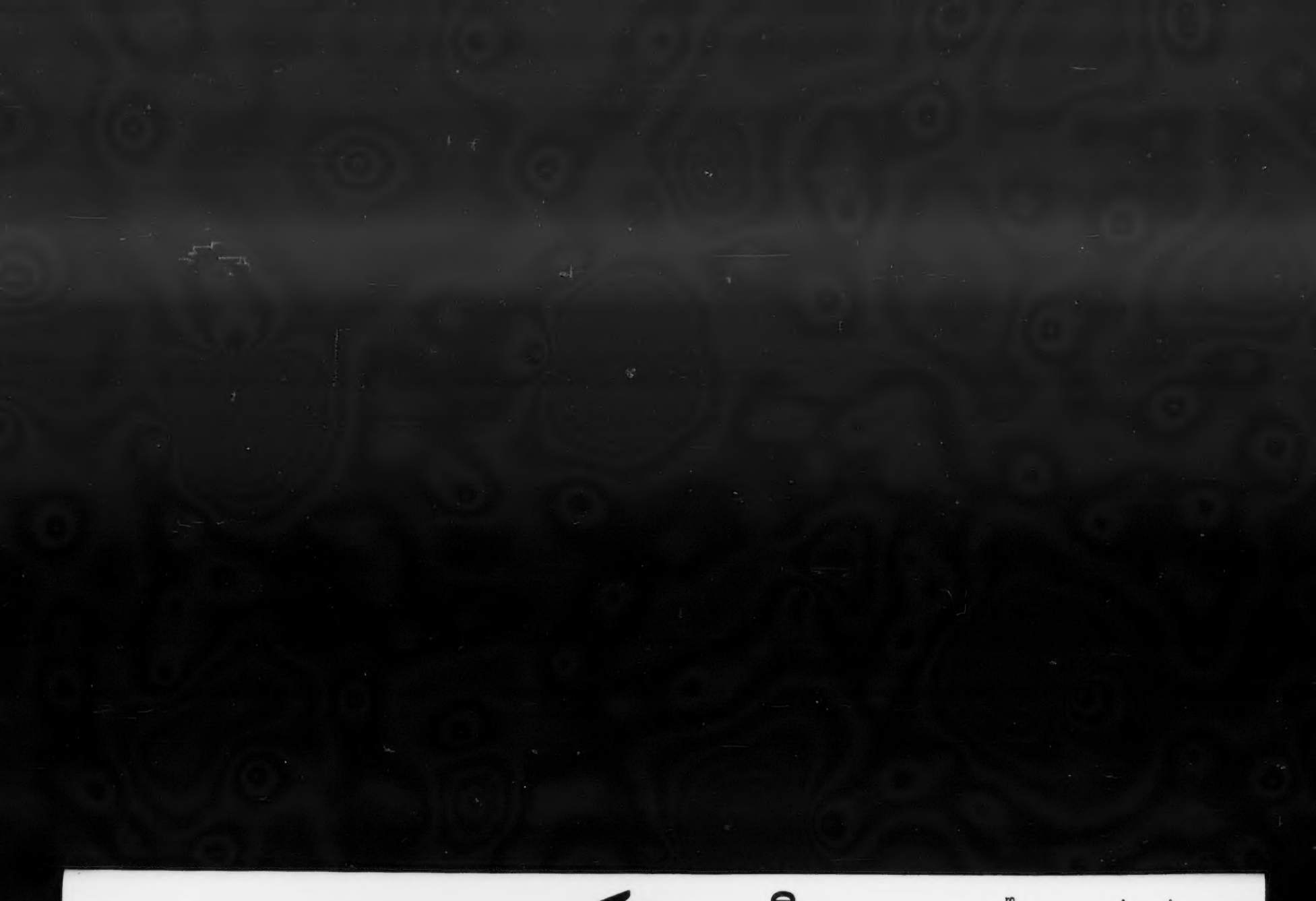

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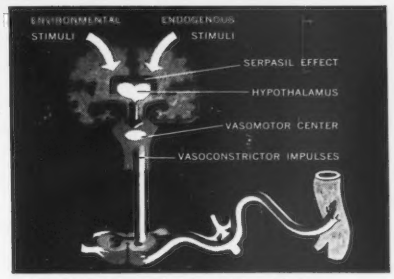

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CIRCULATION

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Editorial

The Surgical Treatment of Acquired Valvular Disease

THE surgical correction of mitral stenosis can be excellent, of aortic stenosis good, of tricuspid stenosis simple. Any or all of these can be corrected at one operation if necessary. The surgical correction of organic insufficiency of these valves is now only palliative. Functional mitral, tricuspid, and pulmonic insufficiency respond to correction of the primary condition. Functional tricuspid stenosis like insufficiency, responds to correction of the associated mitral stenosis.

Pure lesions and all combinations must be considered individually. In each instance, certain relevant pathologic, clinical, and hemodynamic features must be mentioned to clarify the selection of patients.

Mitral Stenosis

Experience with mitral stenosis has clarified its diagnosis, life cycle, surgical risk, and rehabilitation. To define risk, patients suffering from mitral stenosis have been divided into 4 groups broadly defined as follows: Group I: patients with the murmur of mitral stenosis but *no disability;* auscultatory disease of no hemodynamic significance. Group II: individuals with mild *nonprogressive* limitation. Group III: those with pure mitral stenosis and *progressive* symptoms. Compensation is disintegrating. Group IV: patients who are in the terminal or late phases of the life cycle, generally with refractory congestive failure. Often they have irreversible damage to the lung, liver, or myocardium. Ellis has carefully studied the first thousand valvuloplasties performed by Harken's group. The surgical mortality has fallen dramatically. Group III patients had a 0.6 per cent mortality in the second 500 operations. The mortality remained high (20 per cent) for the same period among the group IV patients. Not only has the mortality in group III patients reached an enviable level comparable to other general surgical procedures but rehabilitation is better before there is damage to the lungs, liver, and myocardium. Useless delays are often counseled because of possible rheumatic activity, aortic insufficiency, subacute bacterial endocarditis, and thyrotoxicosis. These diseases are readily established or eliminated beyond reasonable doubt while the patient is being prepared for surgery.

A final echelon of confusion has arisen due to the occurrence of mitral stenosis without a murmur. Happily, this has led to more careful auscultation in better positions and with a variety of stethoscopes so that this event has become less common. Most careful auscultation has clarified ancillary physical evidence of mitral stenosis and conversely has shown that the loudest diastolic murmurs may occur in dominant mitral insufficiency. This loud diastolic murmur of insufficiency is due to the increased amount of blood flowing over the valve during diastole.

Although 530 of the first thousand surgical patients studied by Ellis had atrial fibrillation, this arrhythmia is still mentioned as a surgical contraindication. Incidentally, preoperative reversion to normal sinus rhythm is ill advised, for they often fibrillate again

after surgery. The total risk of embolus is probably less in proceeding directly to operation. It is better to flush out thrombi at operation rather than to risk embolus during medical reversion. After surgery it may be possible to restore normal sinus rhythm permanently.

Valvuloplasty significantly reduces the danger of embolism in mitral stenosis, presumably because stasis is reduced and the appendage is removed. Because repetition of embolization is common, one episode may be a substantial factor in favor of immediate operation. Repeated emboli within a period of a few weeks may constitute an urgent indication for valvuloplasty, and repeated embolization within a space of a few days in spite of anticoagulant therapy defines a surgical emergency unless the patient's general condition precludes surgery. Even in such surgical emergencies embolization has always been stopped by valvuloplasty and coincident appendicectomy.

The danger of embolization at surgery has been reduced by 3 factors. First, flushing the atrium evacuates thrombi from the appendage. Second, occlusion of the cervical vessels for appropriate intervals after fracturing through calcific areas in the valve reduces the chance of cerebral emboli by shunting blood past the brain to silent areas. Third, experience helps the surgeon decide where to fracture in order to avoid mobilizing calcific fragments.

Just as experience has led to better fracture with fewer emboli, it has improved mobilization of leaflets without the production of regurgitation. Indeed, regurgitation may be reduced by valvuloplasty. The propriety of posterior commissural opening is a technical consideration not within the scope of this discussion. There is a place, however, for such fracture or incision. At times this posterior fracture must be avoided to avoid regurgitation; at times it must be used in order to effect satisfactory valvuloplasty. Failure to obtain good valvuloplasty initially is the most common cause for poor surgical results. *Re-operation must be considered when any patient who has had pure mitral stenosis fails to demonstrate or maintain improvement.*

The safe conduct of a patient with severe mitral stenosis through pregnancy is a real medical challenge. A good medical regimen and bed rest will allow most patients with auscultatory disease and many with hemodynamically significant disease to negotiate pregnancy safely. However, there are patients who develop pulmonary edema or congestion and progressive symptoms in the first trimester where pregnancy is unsafe for mother or baby.* A persuasive statistical case can be martialed for the interruption of pregnancy and the correction of mitral stenosis later. This does not take several factors into consideration. First, abortion with subsequent valvuloplasty necessitates 2 operations. Second, experience indicates that valvuloplasty can be carried out safely if the patient has tight mitral stenosis and the pregnancy is in the first trimester, (a greater risk may exist, yet be justified later). Third, religious factors may influence the decision. Fourth, many mothers simply *want their babies.* How one weighs this last factor must be an individual matter.

Three warnings should be sounded in connection with mitral stenosis and pregnancy. The diagnosis of pure mitral stenosis during pregnancy is notoriously unreliable. The increased blood flow of pregnancy over an only slightly roughened valve may suggest stenosis when the disability is actually due to something else. A reliable diagnosis of stenosis before pregnancy is therefore virtually essential for a safe decision. The danger of producing congenital anomalies suggests that the end of the first trimester is best for the correction of stenosis. The pregnancy is also more secure. Finally, delivery by cesarean section is inadvisable after successful valve surgery unless specifically indicated by such factors as cephalopelvic disproportion.

Patients past 50 have been considered too old for valvuloplasty by some clinicians. We

*Specifically, these women would be classified as group III before pregnancy.

have operated on approximately 200 patients between the ages of 50 and 70. These patients have enjoyed results comparable to younger patients. The incidence of heavily calcified valves is higher; the occurrence of other complicating diseases is more prevalent. Thus, if a patient has mitral stenosis, its correction must be considered on its individual merits in that patient.

Aortic Stenosis

There are definite indications for surgical intervention for aortic stenosis. Earlier experience with the valvulotome through the left ventricle was disappointing. The results were not comparable to the transaortic leaflet mobilization. In this operation, a small Ivalon (polyvinyl alcohol) operating tunnel is sutured to the side of the base of the aorta to allow direct digital manipulation. A valvulotome may also be used if necessary. I am convinced that this operation has advantages over available direct-vision procedures. This operation can be careful, deliberate, and meticulous without an open technic per se with hypothermia or pump-oxygenator. It also affords an opportunity to assess valve mobility under conditions of flow. Formidable as many calcific valves look at autopsy, experience indicates that some mobilization is usually possible.

Comparison of surgical patients with patients not having surgery clarifies the place for operation. Among our first 80 modern transaortic operations there have been 13 surgical deaths. Seven operative deaths occurred in the first 20 operations; among the second 20 operations there were 4 deaths; in the last 40 operations there have been but 2 operative losses. Apparently, this operative mortality may now be as low as 5 per cent. Eight late deaths indicate that some patients do not do well. However, more than half return to work. The salvage in this group is striking when compared with a personally observed "control" group of 52 patients who, for one reason or another, failed to have surgery. Of these 52 patients who did not have surgery 47 were dead within 6 months after surgery had been advised.

This formidable experience is a result of the selection of patients largely on the basis of left ventricular failure and also because it includes some patients who succumbed before surgery could be done. Nevertheless, it indicates what a devastating disease aortic stenosis can be when it is hemodynamically significant to the point of left ventricular failure. Left ventricular failure as manifested by progressive dyspnea in spite of adequate medical therapy seems to be an urgent indication for intervention. Persistent angina and troublesome syncope may also justify surgery, although Ellis and his colleagues have shown that some of these patients may survive for years. Contrariwise, left ventricular failure or atrial fibrillation is very ominous. Ellis further found that the onset of pain or syncope during atrial fibrillation or failure was generally followed by death within days or weeks. This better understanding of the life cycle of aortic stenosis interpreted in the light of the results of surgery clearly defines a place for operative intervention. The left heart catheterizations and hemodynamic studies of valve gradients, cardiac outputs, and dye dilutions carried out on many of these patients by Dexter and his group, indicate that this surgery does not compare favorably with valvuloplasty for mitral stenosis. However, even in cases where left heart catheterization is unimpressive, clinical palliation may be excellent.

Aortic and mitral stenosis can be corrected at the same operation if necessary. The severity of aortic and mitral stenosis in combination can best be evaluated by left heart catheterization. Rarely should surgery be performed on patients with multivalvular problems without such studies. This includes not only valve gradients but cardiac output and dye-dilution studies. Formerly, pressures and gradients were measured at the operating table but preoperative left heart catheterization has largely replaced such studies.

Tricuspid Stenosis

The surgical correction of tricuspid stenosis is technically easy but rarely indicated.

Aortic and Mitral Regurgitation

The surgical correction of aortic and mitral regurgitation has not been so successful as that of stenosis. In aortic insufficiency the Hufnagel valve presumably reduces ventricular work, but at the same time, it reduces diastolic perfusion of the coronary arteries. We abandoned this operation some years ago in favor of a direct circumclusion procedure, which reduces the size of the base of the aorta below the coronary ostia. This operation involves careful dissection of the base of the aorta; isolation of the coronary arteries and anchoring a tapered band about the aorta in a zone of leaflet insertion below the coronary ostia. Extensive calcification makes this operation impossible.

Just as the pathologic process in aortic stenosis may limit the quality of surgical repair, some patterns of aortic insufficiency and combinations of stenosis and insufficiency are clearly not amenable to surgical correction where only the existing damaged parts are used. Prosthetic valves must be developed. The objection to the Hufnagel valve is that it reduces diastolic pressure and coronary perfusion because of its position in the descending aortic arch. The obvious answer is to place the valve at the normal valve site. There are serious technical problems in designing such a valve and in placing it properly so as to avoid coronary obstruction and cerebral embolus. This need and these difficulties have again made us look hopefully at a prosthetic aorta containing a valve, originating from the apex of the left ventricle and inserting into the lower thoracic aorta, as suggested by Donovan and Sarnoff. Aortic stenosis constitutes the first place for such a by-pass. With ventricular pressures reduced to normal levels the stenotic orifice would probably cease to have significant function. In free aortic insufficiency or mixed stenosis and insufficiency, a similar by-pass could be used if the natural outflow tract or aortic base were closed. This should not be an insurmountable technical problem.

The surgical correction of *mitral incompetence* has been a troublesome and frustrating pursuit. A review of certain basic hemodynamic and morphologic concepts makes the clinical picture and the surgical challenge clearer. It also forms a basis for reviewing past and present operations. The morphologic lesion in mitral insufficiency may be an absolute or relative loss of valve leaflet substance, or both. The valve may fail to close because of small leaflets or an enlarged annulus. When small leaflets allow regurgitation, it is compensated by a greater volume of ejected blood, and thus greater ventricular chamber size, which in turn may cause an increase in the size of the annulus and greater relative insufficiency. This cycle may also be initiated by primary myocardial disease.

Two other mechanisms in this self-aggravating cycle point the direction for definitive surgery and present palliation. First, there is atrial herniation of the valve ring that causes the most marked incompetence posteriorly. Second, herniation renders the chordae tendineae relatively short and interferes with leaflet closure. The normal position of the mitral annulus is just within the upper portion of the left ventricle. Closure of this valve involves the reduction of annulus size by ventricular systole, the relaxation of the leaflet edges and upward movement of the ventricle and papillary muscles to allow leaflet closure and torsion of the chordae tendineae to secure closure. The leaflets are in direct continuity not only with the annulus but with the atrial endocardium. Any systolic jet impinges most forcibly on the adjacent atrial wall, i.e., the atrial insertion at the posterior atrioventricular groove. This force dilates the atrium posteriorly and displaces the annulus up and over the ventricular rim, producing the direct herniation of the valve complex. As the annulus slides over the ventricular rim, the leaflets are shortened and regurgitation is increased locally, demanding further ventricular dilatation to compensate for increased reflux. Thus a vicious cycle is accelerated. Finally, the upward migration of the valve puts traction on the chordae in one direction and the dilatation of the ventricle pulls them in the

opposite direction. Thus taut, the chordae cannot relax to allow leaflet closure in systole and reflux is again aggravated. All these factors result in an excessive increase in ventricular fiber length, loss of myocardial efficiency, and ventricular failure.

Appreciation of these factors in the production and aggravation of insufficiency indicate the folly of suturing leaflets together to correct regurgitation. If the existing valve components are to be utilized in reconstructing a competent valve, the leaflets must be mobile. The annulus must be replaced to its normal position within the ventricle so that the ventricular action supports closure and the chordae tendineae can relax in systole. As the hernia is reduced and the leaflets are replaced within the ventricle, the posterior shortening of leaflets is corrected.

It is obvious how bed rest may reverse all of these aggravating factors. The reduced stroke volume can reduce chamber size, thus reduce annulus diameter and increase leaflet competence and so on. However, at some point the aggravation perpetuates itself in a malignant form unless it is stopped by some surgical maneuver. This operation must either replace the defective valve or, utilizing existing valve components, correct the deficiencies, i.e., leaflet size, annulus size and position, chordae length, and secondarily, ventricular myocardial fiber length. Formerly attempts were made to substitute substance for relative or absolute leaflet loss by baffles. This was hemodynamically attractive but the incidence of embolus precluded their use in patients early enough for maximal efficiency. In the course of these and other operations, it was noted that mild to moderate degrees of regurgitation could be corrected by digital distortion of the mitral annulus by posterial pressure with the finger *on the outside of the heart in the atrioventricular groove*. This maneuver was even more effective if the atrial wall was invaginated slightly toward the ventricular chamber, thus reducing the valve herniation. This lengthened the leaflets, relaxed the chordae tendineae, and if the annulus was compressed into an ellipse simultaneously, the shortened leaflets could close the orifice still more effectively. This suggested a mechanism of improving mild to moderate regurgitation. The problem was to get a substance to maintain the same force as the finger. Various substances including lucite, Ivalon (polyvinyl alcohol), and steel wire were used. None of these materials seem to maintain their position as well as Gel-Foam® compressed to a hard, nonabsorbable state. As this extrinsic baffle is placed, the correction of regurgitation is noted by a finger in the heart. Experience with more than 200 of these extrinsic baffles indicates that the procedure is simple, safe, and useful in correcting those mild to moderate degrees of incompetence often encountered at valvuloplasty for stenosis.

When the dominant lesion is marked regurgitation, the available surgical maneuvers leave much to be desired. Open correction is encouraging but is still in the experimental stage. D'Avila and Glover have developed a circumelusion operation that is attractive in several aspects. It cannot reduce the herniated complex, thus the disadvantage of relative shortening of the chordae tendineae remains. There are additional technical and clinical reasons that temper enthusiasm for this procedure. The markedly disabled patient who should be benefited if a procedure is sound, does not tolerate this circumelusion. We abandoned this procedure 2 years ago. D'Avila and Glover have now tried this circumelusion on a more favorable risk group, and report salutary effect. If their reasons for moving to good risk patients were valid, operations on patients with terminal aortic valve disease should fail; such has not been our experience. One can only conclude that definitive surgery for severe degrees of mitral insufficiency has not yet been established.

In conclusion, this wide spectrum of operations complicates the selection of patients. The old platitude "the patient is doing very well" becomes only a relative comment. If

pure mitral stenosis is causing no limitation and is not damaging the lungs or myocardium by pulmonary hypertension, "doing well" is acceptable. We are not ready for prophylactic valvuloplasty as in closure of the patent ductus. Valvuloplasty is not quite curative; indeed, when poorly done, stenosis may recur. However, as soon as the patient with mitral stenosis "begins to have to give up things in life," he is no longer "doing well" and surgery must be considered. When symptoms are progressive, surgery must be urged. The place for surgery in pregnancy, after embolus, and in the terminal phases of the life cycle of disease has been clarified. "Following a patient," from group III with an operation risk of 0.6 per cent into group IV, with a 20 per cent mortality, is condemned.

These new medical responsibilities have sharpened all diagnostic technics. The history must discover concealed but serious limitations such as those in sex activity. Progressive dyspnea must be recognized. Dyspnea that does not seem to be progressive may appear static due to self-imposed or physician-imposed restriction. If the patient admits of no limitation, one must detect the limitation unrecognized because of insidious onset. On the other hand, one must not be confused by limitation imposed by a physician, or so-called iatrogenic disability. In cases where the disability is difficult to assess, right or left heart catheterization may help measure the hemodynamic disturbance.

Aortic stenosis may cause angina, syncope, atrial fibrillation, and all degrees of left ventricular failure. Surgery has a place when the symptoms are progressive, when the heart size increases, or when the left heart catheterization shows a critical valve size or an intolerable gradient. Surgery is urgently indicated when there is left ventricular failure or progressive dyspnea in spite of a good medical regimen. Minor degrees of aortic insufficiency associated with stenosis may improve with good aortic valvuloplasty.

In aortic insufficiency, the surgical treatment is incomplete and only palliative. This makes recognition of the role of surgery all the more difficult. There are minor hemodynamic problems that certainly are much better handled by waiting for better operative procedures. Rigid medical treatment may be life-saving. The effective "medical regimen" involves measured salt restriction, proper use of digitalis, diuretics, drug prophylaxis, and work tolerance assay and regulation. Overt congestive failure is late and ominous. A diuretic response, before congestive failure becomes obvious on physical examination, is a critical method of detecting occult failure. In the presence of overt or latent failure, surgery must be considered.

Severe mitral regurgitation will be better treated by a more definitive operation in the future but minor degrees of regurgitation must not prevent a patient from receiving valvuloplasty for stenosis. In the course of the surgery, available therapy or "strategic retreat" with the extrinsic baffle is useful. The simplest operation for severe pure mitral regurgitation appears to be D'Avila's and Glover's mitral circumclusion; the most definitive: open operation.

The surgical correction of acquired valvular disease is routinely followed by meticulous medical treatment for some months. This course is important during the period of myocardial adjustment to new hemodynamic factors. This need does not mean that surgery has failed any more than the persistence of a murmur. The physician will do well to reduce the medical program gradually.

Surgery has complicated but stimulated the whole field of cardiology.

DWIGHT E. HARKEN

Relationship of Degree of Atherosclerosis of Internal Carotid System in the Brain of Women to Age and Coronary Atherosclerosis

By MALCOLM D. WINTER, JR., M.D., GEORGE P. SAYRE, M.D., CLARK H. MILLIKAN, M.D., AND NELSON W. BARKER, M.D.

Cerebral infarction currently is the third leading cause of death in the United States. Since atherosclerosis of the cerebral arteries is the basis for the majority of strokes, the authors undertook to define more accurately the distribution of such atherosclerosis, its relation to coronary atherosclerosis, and its relation to such other factors as hypertension, obesity, and cerebral infarction. The results of their study are presented here.

CEREBRAL infarction currently is the third leading cause of death in the United States.[1] The incidence of "cerebral vascular accidents" in various necropsy series has varied between 5 and 24 per cent.[2] Since atherosclerosis of the cerebral arteries is the basis for the majority of strokes, the present study was undertaken in an effort to define more accurately the distribution of such atherosclerosis, its relation to coronary atherosclerosis, and its relation to such other factors as hypertension, obesity, and cerebral infarction.

Histologically, cerebral arteries differ from arteries throughout the rest of the body in several respects. They have a very well-developed internal elastic membrane, but an external elastic membrane is completely lacking. Their medial and adventitial coats are thinner and less well developed than those of other arteries. Very early in life the internal elastic membrane begins to split into 2 laminae at points where vessels bifurcate.[3] The external lamina is thin and smooth, forming the boundary between the intima and media. The internal lamina is irregular and thick, often containing a number of clefts. With aging, the arterial walls thicken in proportion to their increased caliber. The internal elastic membrane splits in other areas at points away from bifurcations, and focal intimal thickening at bifurcations increases. From the age of 20 years on, ruptures may occur in the internal elastic membrane, usually in its outer lamina. Difficulty arises in separating changes due exclusively to age from those due to some pathologic process.

REVIEW OF LITERATURE

Wolkoff[3] in 1933 studied specimens from 98 individuals ranging from 2 to 81 years of age; he opened up the arterial system of each brain by longitudinally incising the cerebral arteries in situ out to their smallest ramifications. He found 3 types of atherosclerotic lesions: lipid spots, lipid plaques, and fibrous plaques. Grossly lipid spots first became evident during the middle of the fourth decade of life. Staining the arteries with Sudan III made them visible near the end of the third decade. At first only 1 to 3 small, irregular, round spots ranging in size from that of a pinhead to that of a millet seed could be found per brain. During the fourth decade the number and size increased although some specimens were still completely free of them. When present they tended to stretch out in a longitudinal direction and frequently merged with each other. The

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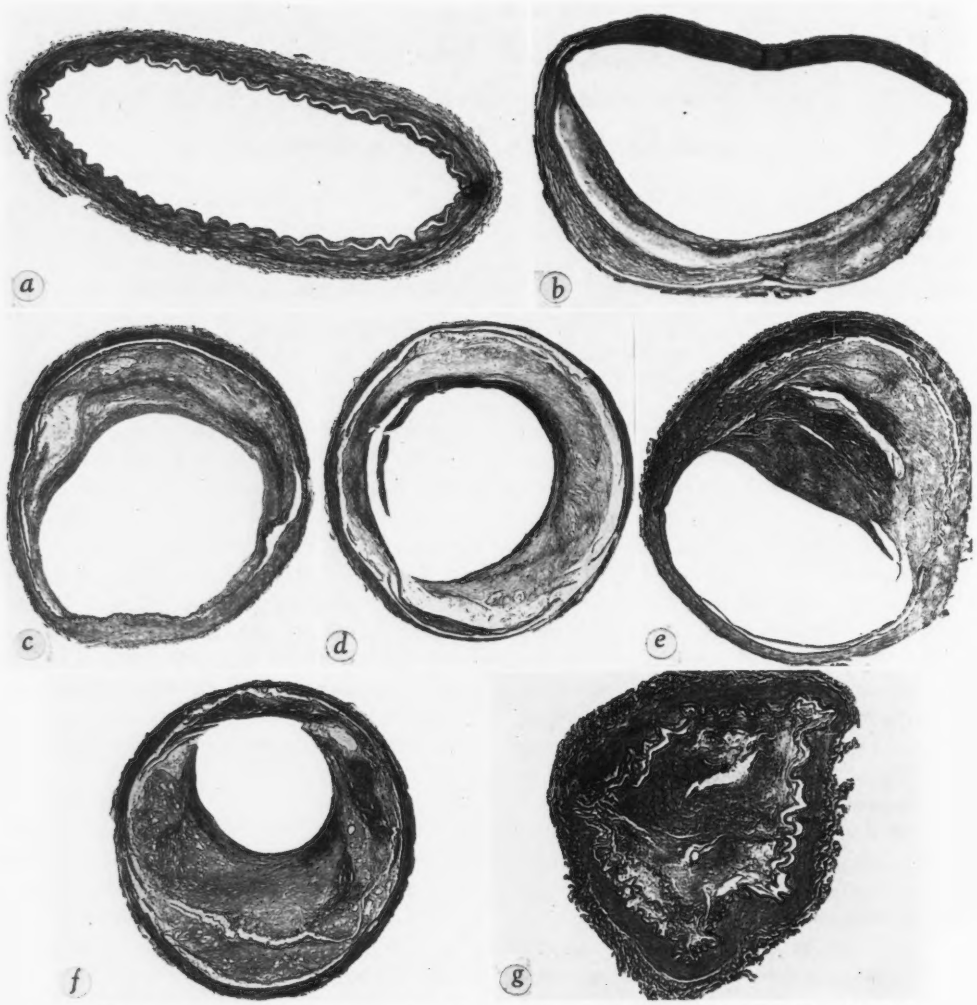


FIG. 1. Sections representative of grades of atherosclerosis. *a*. Grade 1 (× 30). *b*. Grade 1.5 (× 20). *c*. Grade 2 (× 15). *d*. Grade 2.5 (× 20). *e*. Grade 3 (× 30). *f*. Grade 3.5 (× 20). *g*. Grade 4 (× 40).

lipid content of some of them had increased enough to cause them to stand out from the intimal surface—these Wolkoff classified as lipid plaques. During the fifth decade lipid spots were present in all cases but were of differing number and stage of development. Fibrous plaques were found in 2 cases (ages 46 and 47), and consisted of fine whitish thickenings over the central portions of lipid foci. From the sixth decade on, lipid spots and plaques were found in all cases; fibrous plaques were found more and more frequently and in greater numbers with larger dimensions. Narrow lipid streaks frequently departed from a pronounced lipid or fibrous plaque and extended in a longitudinal direction along the artery. Fibrous plaques reached 1.5 to 2 inches in length, usually being longitudinally placed. Frequently they were fused with one another and occu-

pied a large part of the entire intimal surface of the artery in question. Their lipid content was large and their fibrous component greatly thickened.

Both Fisher[4] and Wolkoff[3] found the large arteries at the base of the brain to be involved with atherosclerosis earlier and to a more severe degree than were their more distal branches. The carotid and basilar systems were usually approximately equally involved, although exceptions did occur.

Duff and McMillan,[5] and Wolkoff,[3] have expressed the view that atherosclerosis affects the cerebral arteries much later in life than it affects the aorta and coronary arteries. Fisher,[4] on the other hand, has stated that while in most instances cerebral atherosclerosis is somewhat less advanced than atherosclerosis elsewhere, qualitatively its severity roughly parallels that found in other organs. He has said that it is wrong to emphasize differences in cerebral atherosclerosis from atherosclerosis found elsewhere.

Method and Material

In 1949 Ackerman[6, 7] studied the degree of coronary atherosclerosis in women 30 through 89 years of age. He examined 100 hearts in each of 6 decades. They represented a consecutive series running retrogradely from the end of 1946, except that for the age period 80 through 89 years the series was extended forward into 1948 in order to obtain enough specimens. All causes of death were included.

In the current study all available brains from cases used in Ackerman's study were employed for the evaluation of cerebral atherosclerosis. A total of 239 brains were satisfactory for this purpose. The arteries studied were those of the supraclinoid carotid system and included the following: 1. The segments of the supraclinoid portions of the internal carotids which remained attached to the brain at the time of its removal from the skull. 2. The middle cerebrals to the point of their trifurcation or to the point where they had divided into 3 major branches. 3. The anterior cerebrals to the anterior margin of the genu of the corpus callosum.

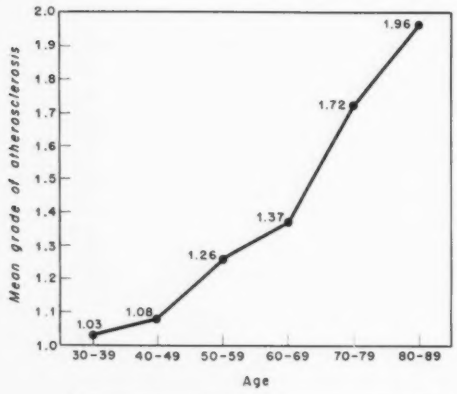
The internal carotid segments varied greatly in length and were sometimes missing completely because of the difficulty encountered in cutting them at their exact point of emergence from the dura prior to removal of the brain from the skull. Occasionally the middle and anterior cerebral arteries were also either partly or entirely missing. If any portion of an artery was present, it was used in the study. If more than half of the supraclinoid portion of the internal carotid system was absent, that brain was omitted from the study.

Table 1.—*Grade of Atherosclerosis Correlated with the Percentage of Lumen Obliterated by Atheromatous Plaque*

Grade	Obliteration of lumen, per cent
1	0 —12
1.5	12.5—24
2	25 —37
2.5	37.5—49
3	50 —74
3.5	75 —99
4	100

The maximal degree of atherosclerosis found in each artery was determined. This was accomplished by sectioning each artery at intervals of 3 to 5 mm. whenever gross atherosclerosis was evident. The 1 or 2 sections from each artery having the greatest degree of atherosclerosis were graded grossly and saved to be made into histologic sections. Later each section was graded microscopically. Gross and microscopic grades of the same section often differed. Frequently the microscopic grade was lower than the gross grade. Often this was due to the microscopic section having been cut a short distance from the area of maximal atherosclerosis. In other instances it was due to contraction of the arterial wall giving a falsely high impression of the degree of atherosclerosis when viewed grossly. In cases in which arteries were contracted, only the microscopic grade was used. In all others, the highest grade, microscopic or gross, was the one used in the study.

The actual grading was on the basis of grade 1 (minimal atherosclerosis) to grade 4 (complete atherosclerotic closure of the lumen). The photomicrographs presented in figure 1 are of representative sections of various grades of atherosclerosis used in this study. The grading is identical to that used by White[8, 9] in male hearts and Ackerman[6, 7] in female hearts. Grades were correlated with percentage of luminal obliteration caused by the atheromatous plaque (table 1). In collapsed or contracted vessels the grade of atherosclerosis was determined from an estimation of what the wall-to-lumen ratio would have been in their expanded form. When a vessel was occluded by a blood clot, only the underlying atherosclerosis was considered. In occasional instances, as



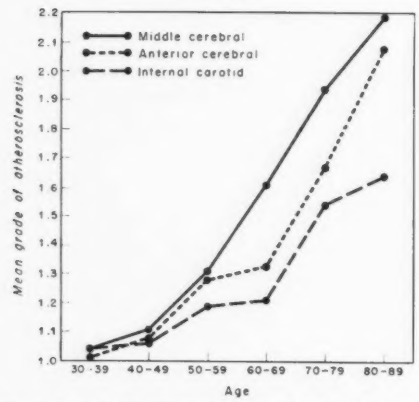


FIG. 2 *Top.* Mean cerebral atherosclerosis by decade of age.

FIG. 3 *Bottom.* Mean atherosclerosis by major cerebral arterial branch by age. Right and left combined.

exemplified by the artery shown in figure 1*g*, the atherosclerotic plaque may represent an organized thrombus. Because of the difficulty in separating organized thrombi from fibrotic atheromatous plaques, differentiation of the two was not attempted. As with Ackerman's series of cases, the ages were rotated during the grading process and were unknown at the time of grading.

The computations to develop the results of the study were as follows: Six numbers representing the highest grade of atherosclerosis in each of 6 arterial branches were added and the sum divided by 6 to determine the *mean grade of atherosclerosis for each brain.* Then all of the latter grades in each decade were added and the sum divided by the number of cases in that decade to determine the *mean grade of cerebral atherosclerosis for that decade.* Next, the highest of the 6 highest grades for each brain was recorded and this

TABLE 2.—*Mean and "Maximal" Cerebral Atherosclerosis for Each Decade of Life*

Age, years	Cerebral atherosclerosis			
	Mean grade	S. D.	Cases	"Maximal" grade
30–39	1.03 ± .01	0.09	50	1.12
40–49	1.08 ± .04	0.25	45	1.23
50–59	1.26 ± .06	0.45	48	1.61
60–69	1.37 ± .10	0.53	26	1.79
70–79	1.72 ± .09	0.61	37	2.54
80–89	1.96 ± .12	0.67	33	2.66

was considered to represent the *"maximal" grade of atherosclerosis for that brain;* all the latter grades in each decade were added and the sum divided by the number of cases in that decade to determine the *"maximal" grade of atherosclerosis for that decade.* Similarly, the highest grades of atherosclerosis for the internal carotid, anterior cerebral, and middle cerebral arteries respectively in each decade were averaged to determine the *mean grade of cerebral atherosclerosis by major arterial branch by decade.*

In addition to the grading of cerebral atherosclerosis in each case, the heart weight, the nutritional state, the principal and contributing causes of death, and the nature of the cerebral lesions found were recorded after a survey of each protocol. All instances of atrial or ventricular mural thrombi, rheumatic heart disease, hypertensive heart disease, or myocardial infarction were tabulated.

RESULTS*

1. Relationship of Degree of Cerebral Atherosclerosis to Age. Mean Grade of Cerebral Atherosclerosis. The results of determination of the mean grade of cerebral atherosclerosis are plotted in figure 2 and are listed with their standard deviation, standard error, and sample size in table 2. These values are lower than those usually reported in describing degrees of cerebral or coronary atherosclerosis This is because the value derived for any individual case is an average of 6 highest values and not the single highest value for all cerebral arteries, as is usually recorded.

*In order to simplify terminology, atherosclerosis in the supraclinoid portion of the carotid circulation will hereinafter be referred to simply as cerebral atherosclerosis. The ordinate of all the following graphs represents the mean grade of atherosclerosis present.

TABLE 3.—*Comparison of Minimal and Severe Cerebral Atherosclerosis with Coronary Atherosclerosis Found by Decade of Age**

Age	Total cases	Atherosclerosis							
		Mean grade 1				Mean grade 2 or over			
		Cerebral		Coronary		Cerebral		Coronary	
		No.	%	No.	%	No.	%	No.	%
30–39	50	37	74	23	46	0	0	1	2
40–49	45	24	53	13	29	1	2	4	9
50–59	48	22	46	8	17	5	10	3	6
60–69	26	8	31	3	12	3	12	5	19
70–79	37	2	5	0	0	13	35	14	38
80–89	33	1	3	0	0	13	39	15	45

* Patients with mean atherosclerosis between grade 1.0 and grade 2.0 are not included.

For comparison, averages were also calculated from the latter values and are listed in table 2 under the heading "maximal" cerebral atherosclerosis.

Mean grade of cerebral atherosclerosis by decade of life steadily increases from 1.03 in the fourth decade to 1.96 in the ninth. Progression of the atherosclerotic process appears to become more rapid after the fourth decade.

The percentage of brains in each decade with minimal (grade 1.00) atherosclerosis decreases from 74 per cent in the fourth decade to only 5 per cent in the eighth and 3 per cent in the ninth (table 3). On the other hand, the percentage of brains with severe atherosclerosis, that is, having a mean of grade 2.00 or more, is zero in the fourth decade and increases from 2 per cent in the fifth decade to 39 per cent in the ninth.

Mean Grade of Cerebral Atherosclerosis by Major Arterial Branch by Decade. Since the grades of atherosclerosis on the right and left sides were about the same, they were averaged together and the values obtained for the intracranial portion of the internal carotid, the middle cerebral, and the anterior cerebral arteries by decade were plotted (fig. 3). There is some increase in atherosclerosis from decade to decade in each of the 3 pairs of arteries. After the fourth decade, the middle cerebral arteries tend to show the highest grades of atherosclerosis, and the internal carotid arteries the lowest. Both the internal carotid and anterior cerebral arteries show a somewhat uneven progression of their atherosclerosis.

2. Comparison of Cerebral Atherosclerosis and Coronary Atherosclerosis. Since similar methods were used to grade the atherosclerosis present in the hearts and brains of this series of necropsies, the mean grades of cerebral and coronary atherosclerosis were determined. In each series of cases the final mean was derived by averaging the highest grades of atherosclerosis found in each of 6 vessels. The thicknesses of coronary and cerebral arterial walls differ, but grading was performed in such a manner that it was not affected by this factor. The length and caliber of the 2 sets of vessels were not the same and therefore some differences between the relative values of the final figures for the 2 sets are to be expected.

Comparison of Severity and Rates of Progression of Cerebral and Coronary Atherosclerosis with Age. According to the methods used, coronary atherosclerosis in each decade is more severe than cerebral atherosclerosis in the same decade (fig. 4). It progresses steadily until the ninth decade, when its rate of progression markedly decreases. The curve for cerebral atherosclerosis, except for the fourth and ninth decades, tends to follow the same rate of climb as the curve for coronary atherosclerosis in the same series

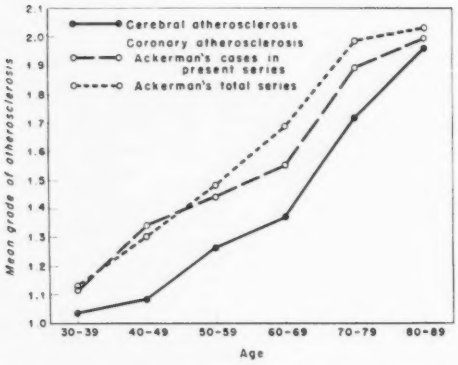
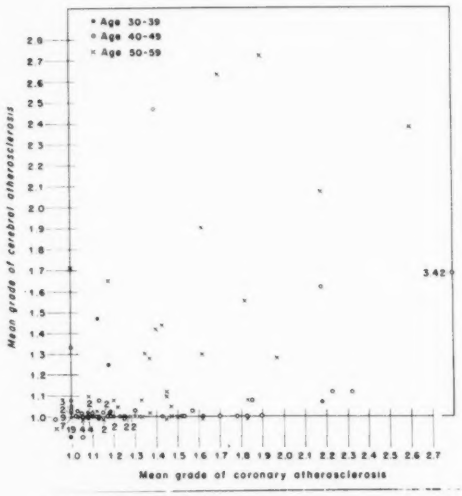


FIG. 4. Grades of mean cerebral and coronary atherosclerosis according to age.

of cases. Coronary atherosclerosis increases steadily through the eighth decade and then tends to level off. Cerebral atherosclerosis increases only slightly from the fourth to the fifth decade, but then increases steadily up through the ninth decade when it becomes almost as severe as coronary atherosclerosis.

Comparison of Grades of Cerebral and Coronary Atherosclerosis in Individual Cases. Figures 5 and 6 are scattergrams that compare coronary and cerebral atherosclerosis in each case. Although there are objections to the validity of quantitatively comparing the mean values derived in each case with each other, the variation in values found in different cases in each system is accurate, since grading of each system is consistent within itself. Also, one can assume with a fair degree of certainty that the finding of grade 1 atherosclerosis is comparable between the 2 arterial systems in each case. The scattergrams vividly demonstrate that the degree of atherosclerosis in the cerebral arteries may vary widely from that in the coronary arteries in any one case. Extreme examples are found in one patient having grade 2.9 coronary atherosclerosis and only grade 1.02 cerebral atherosclerosis, and in another patient having grade 1 coronary atherosclerosis and grade 2.3 cerebral atherosclerosis. Thus in individual cases there is very little correlation between degrees of atherosclerosis in the 2 systems. In the earlier decades a fairly



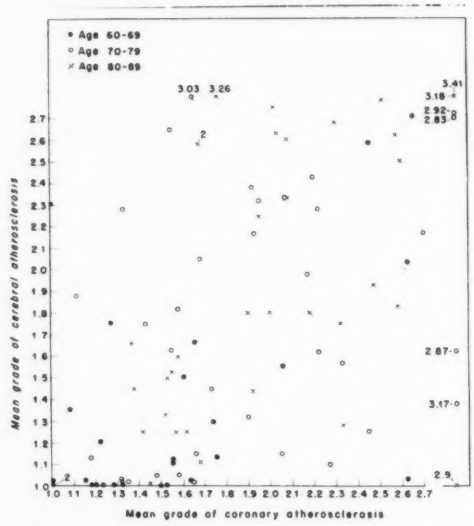


FIG. 5 *Top.* Scattergram comparing mean grades of coronary and cerebral atherosclerosis in each case: ages 30 to 59.

FIG. 6 *Bottom.* Scattergram comparing mean grades of coronary and cerebral atherosclerosis in each case: ages 60 to 89.

large proportion of the patients have no atherosclerosis in either system or have but one system involved (table 4). As an example, in the fourth decade 38 per cent of the patients have no evidence of either coronary or cerebral atherosclerosis, while 36 per cent have evidence of coronary atherosclerosis

TABLE 4.—*Patients in Each Decade without Atherosclerosis in Either System, with Only Coronary Atherosclerosis, with Only Cerebral Atherosclerosis, and with Both*

Age, years	Total cases	Atherosclerosis							
		None		Coronary only		Cerebral only		Both	
		No.	%	No.	%	No.	%	No.	%
30–39	50	19	38	18	36	4	8	9	18
40–49	45	9	20	15	33	4	9	17	38
50–59	48	7	15	15	31	1	2	25	52
60–69	26	2	8	6	23	1	4	17	65
70–79	37	0	0	2	5	0	0	35	95
80–89	33	0	0	1	3	0	0	32	97

without any cerebral atherosclerosis as compared to only 8 per cent in which the reverse is found. The percentage of patients without atherosclerosis in either system steadily declines until the eighth decade, when all patients have some degree of atherosclerosis in their coronary systems. Some patients without cerebral atherosclerosis are present in all decades.

Comparison of Ages at Onset of Coronary and Cerebral Atherosclerosis. By listing the percentage of the sample in each decade involved with minimal (grade 1) or severe (grade 2 or more) cerebral and coronary atherosclerosis, a comparison can be made between the onsets and to a lesser extent the severity of atherosclerosis in the 2 systems. Table 3 shows that only a quarter of the patients in the fourth decade are affected with more than minimal cerebral atherosclerosis while about half of them have more than minimal coronary atherosclerosis. Severe grades of cerebral atherosclerosis start occurring a decade later than do severe grades of coronary atherosclerosis. By the ninth decade 45 per cent of patients have severe coronary atherosclerosis compared to 39 per cent with severe cerebral atherosclerosis.

3. Relationship of Cerebral Atherosclerosis in Various Age Groups to Cerebral Infarction. Sixty cerebral infarcts were found in the 239 necropsies. Cerebral infarcts of all kinds were included: recent, healed, small, large, miliary, and focal. These cases were separated from the remainder and both the

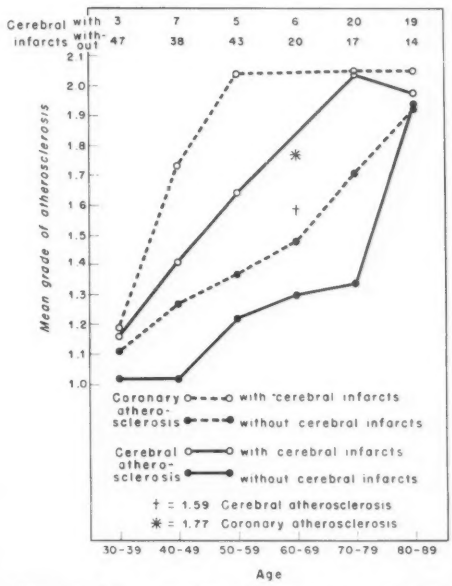


FIG. 7. Mean grades of cerebral and coronary atherosclerosis according to age in patients with cerebral infarcts.

mean and "maximal" grades of cerebral and coronary atherosclerosis were calculated and compared with corresponding data from patients without infarcts (fig. 7 and table 5). One half of the 60 patients with cerebral infarcts had less than grade 2 cerebral atherosclerosis. A high proportion of these patients with low grades of atherosclerosis had only miliary infarcts.

Cerebral and Coronary Atherosclerosis and Cerebral Infarction. As might be expected,

TABLE 5.—*Cerebral Atherosclerosis in Patients with and without Cerebral Infarcts**

Age, years	Infarcts absent			Infarcts present		
	Cases	Grade		Cases	Grade	
		Mean	"Maximal"		Mean	"Maximal"
30–39	47	1.02	1.12	3	1.18	1.70
40–49	38	1.02	1.11	7	1.41	1.90
50–59	43	1.22	1.55	5	1.64	2.16
60–69	20	1.30	1.75	6	1.59	2.38
70–79	17	1.34	1.99	20	2.04	2.95
80–89	14	1.94	2.64	19	1.98	2.94

* See text for definitions of mean and "maximal."

brains having evidence of cerebral infarcts as a group have a higher degree of atherosclerosis than those without infarcts (fig. 7). The difference between patients with and without cerebral infarcts is most pronounced when only the highest of the 6 maximal values determined in each case is used in deriving each group's average. Coronary atherosclerosis is also higher in patients with cerebral infarcts. The differences become less marked in the ninth decade.

4. Role of Thromboembolic Phenomena in Cerebral Infarction. Of the 239 patients studied, 15 had left-sided mural thrombi in their hearts. Nine of the 15 had cerebral infarcts. Of these 9, 3 had complete absence of cerebral atherosclerosis. The others all had high grades of cerebral atherosclerosis (mean 2.28).

5. Relationship of Heart Weight and Hypertensive Heart Disease to Cerebral Atherosclerosis. Cerebral Atherosclerosis and Heart Weight. Ackerman[6, 7] compared heart weight with coronary atherosclerosis. Since the weight beyond which a heart is to be considered enlarged is not definite, he used 3 different dividing points, namely 300 Gm., 350 Gm., and 400 Gm., and computed data on coronary atherosclerosis in hearts whose weights were over or under each of these dividing points. No matter which one was used, coronary atherosclerosis was found to be more severe in the heavier hearts.

Table 6 demonstrates the relationship between heart weight and cerebral atherosclerosis on the basis of the same 3 heart-weight dividing points used by Ackerman. These data fairly consistently show that individuals with heavy hearts have more cerebral atherosclerosis than those with lighter hearts. This is true in the younger decades as well

TABLE 6.—*Relationship of Heart Weight to Cerebral Atherosclerosis*

Age, years	Normal		Hypertension		Difference, %
	Hearts of given weight	Cerebral sclerosis, mean grade	Hearts of given weight	Cerebral sclerosis, mean grade	
	100–299 Gm.		300 Gm. or more		
30–39	29	1.02	21	1.02	0
40–49	21	1.01	24	1.15	14
50–59	15	1.08	33	1.34	25
60–69	6	1.35	20	1.37	2
70–79	11	1.43	26	1.84	29
80–89	8	1.70	25	2.05	20
	100–349 Gm.		350 Gm. or more		
30–39	39	1.01	11	1.08	6
40–49	36	1.02	9	1.33	31
50–59	28	1.08	20	1.51	40
60–69	13	1.29	13	1.44	12
70–79	19	1.48	18	1.97	33
80–89	15	1.87	18	2.04	9
	100–399 Gm.		400 Gm. or more		
30–39	44	1.02	6	1.06	3
40–49	39	1.02	6	1.49	46
50–59	36	1.12	12	1.69	51
60–69	16	1.37	10	1.36	0
70–79	28	1.63	9	2.00	23
80–89	23	1.89	10	2.12	12

TABLE 7.—*Cerebral Atherosclerosis and Hypertensive Heart Disease*

Age, years	Hypertensive		Normotensive	
	Cases	Cerebral sclerosis, mean grade	Cases	Cerebral sclerosis, mean grade
30–39	5	1.05	45	1.02
40–49	7	1.43	38	1.02
50–59	15	1.56	33	1.12
60–69	7	1.31	19	1.39
70–79	16	2.03	21	1.48
80–89	17	2.12	16	1.79

as the older ones, and is true whether the dividing line between normal and hypertrophied hearts is taken at 300, 350, or 400 Gm. The small change noted in patients with hearts weighing more than or less than 300 and 400 Gm. in the seventh decade may be attributable to the small number of cases (26) in the age group.

Cerebral Atherosclerosis and Hypertensive Heart Disease. A diagnosis of hypertensive heart disease was made when hearts without congenital or valvular disease weighed more than normal in relation to body weight as determined by the method of Smith.[10] Table 7 compares cerebral atherosclerosis in cases in which hypertensive heart disease was encountered at necropsy with cerebral atherosclerosis in the remaining cases studied in each decade. The mean grade of cerebral atherosclerosis in normotensive subjects remains the same during the fourth and fifth decades. It then climbs from 1.02 in the fifth decade to 1.79 in the ninth decade. Hypertensive patients have nearly the same grade of cerebral atherosclerosis in the fourth decade as normotensive subjects. By the fifth decade their mean grade of atherosclerosis has climbed sharply to 1.43, and by the ninth decade it has risen to 2.12. After the fourth decade, patients having hypertensive heart disease develop cerebral atherosclerosis earlier and to a more severe degree than do those whose hearts show no evidence of long-standing hypertension. In the seventh decade only 7 patients with hypertensive hearts were available for study, and their mean cerebral atherosclerosis is only 1.31. Since this value is so out of line with the others, it is thought to be due to sampling error.

6. State of Nutrition and Cerebral Atherosclerosis. Patients were subdivided into obese, average, and underweight groups according to the subjective impressions recorded at necropsy. Grades of cerebral atherosclerosis by decade of age were derived for each group; no differences were readily apparent.

DISCUSSION

The concept that atherosclerosis steadily progresses with age was modified by White[8, 9] in 1948, when he demonstrated that in necropsy cases coronary atherosclerosis in males progressed through the sixth decade and then tended to level off. The next year Ackerman[6, 7] in a similar study demonstrated that coronary atherosclerosis in females progressed through the eighth decade before leveling off. Findings in the present study indicate that cerebral atherosclerosis of the supraclinoid carotid system in females continues to progress through the ninth decade.

In several instances, graphs in this series of patients have shown atherosclerosis to progress to a certain level and then remain at about the same level throughout the remaining decades. This may mean that death is more likely to occur when atherosclerosis reaches this level. It does not mean that the atherosclerotic process continues to increase to a certain age and then slows down. Rather, it is an indication of the type of data derived from a series of necropsy cases. If it were possible to do the same type of study in living individuals and follow them from decade to decade, an entirely different set of curves would likely result.

Cerebral atherosclerosis severe enough to narrow the lumen of a vessel occurred in 26 per cent of the cases in the fourth decade (table 3). Wolkoff[3] noted that lipid plaques first began to occur in the fourth decade. Comparison of his classification with the present one is not possible. However, lipid plaques probably represent the first stage of arterial narrowing. Lipid spots as described

would not narrow an arterial lumen. Wolkoff found that lipid plaques were present in all cases by the sixth decade. By the sixth decade in the current series, arterial narrowing was found in only 54 per cent of cases.

In the present study atherosclerosis developed less rapidly in the intracranial portions of the internal carotid arteries than in either of their 2 branches. This is best explained by their very short length. If the segments of the middle cerebral arteries had been shortened so as to have been equal in length to the supraclinoid portions of the internal carotid arteries, their mean atherosclerosis would have been much lower than that recorded. That this is not the entire answer, however, is shown by the fact that the middle cerebral arteries have more atherosclerosis than the anterior cerebral. The segments of the anterior cerebral artery were 2 to 3 times as long as those of the middle cerebral arteries. Probably of more importance than the actual grade of atherosclerosis for each pair of branches are the characteristics of their curves when plotted against age. In every instance the grade of atherosclerosis is low in the fourth decade and then increases rapidly. In the anterior and middle cerebral arteries the increase continues through the ninth decade. Internal carotid atherosclerosis also continues to increase but at a slower rate.

The wide variation in degree of atherosclerosis between the cerebral and the coronary blood vessels in any one case may be striking. Since atherosclerosis is a spotty disease, these findings may be explained simply by the hit-or-miss pattern of severe degrees of atherosclerotic narrowing found throughout the body. However, the degrees of atherosclerosis in different arterial systems, at least in some instances, may be determined by different factors. In chickens atherosclerosis in the coronary vessels is inhibited by estrogen administration, while atherosclerosis in the aorta is unaffected.[11] Whether or not similar influences affect human cerebral and coronary arterial systems has not been determined.

The exact mechanisms by which cerebral infarcts are produced have not been fully elucidated. Cerebral blood flow is determined by blood pressure and vascular resistance. The latter may change uniformly throughout the cerebral vascular bed so that relative blood flow to all parts of the brain remains the same. Atherosclerosis is one process that may interfere with this change, resulting in diminished blood flow to certain parts. If impairment is severe enough, infarction results. This view is supported by the finding of more severe degrees of cerebral atherosclerosis in the group of patients with cerebral infarcts and also by the finding of a greater difference between "maximal" values for the 2 groups than between mean values.

Interesting changes in the mean values for cerebral and coronary atherosclerosis are evident when patients are divided according to whether or not they have had cerebral infarcts. The curve for cerebral atherosclerosis in females with cerebral infarcts becomes similar to that for coronary atherosclerosis in Ackerman's series of female hearts in that it rises steadily from the fourth through the eighth decade and then levels off. The curve for coronary atherosclerosis in females with cerebral infarcts becomes similar to that for coronary atherosclerosis in White's series of male hearts, in that it rises through the sixth decade and then levels off. Cerebral atherosclerosis in females without cerebral infarcts occurs only occasionally before the sixth decade. From the sixth through the eighth decade it increases at a moderate rate, becoming severe in the ninth decade, so that it differs little from that in patients with cerebral infarcts.

Of the 60 patients who had cerebral infarcts, only 9 had evidence of mural thrombi in the heart. The finding of only 3 out of the 60 patients with strokes who had no cerebral atherosclerosis and who had a possible source for cerebral emboli is quite striking. In 1 of these patients infarcts were small and multiple. In the other 2 they were large. If the assumption that these 3 patients had cerebral emboli is made, the incidence of cerebral em-

bolization in 60 patients with strokes is 5 per cent or greater. This is similar to the incidence of 4.6 per cent in Towbin's[12] series of 525 state hospital patients with organic disease of the brain.

Since hypertension is known to affect the severity of atherosclerosis, and since it is extremely common in patients with strokes, a higher degree of cerebral atherosclerosis in patients with hypertension is to be expected. In this series a total of 67 patients died with hypertensive heart disease and 60 with cerebral infarcts; 34 had both.

Correlating state of nutrition with severity of atherosclerosis is difficult because of the variety of factors that enter into the evaluation. A patient's terminal state of nutrition is often different from that during health. Determination of state of nutrition itself is open to wide margins of error. No correlation could be found in this series.

Summary and Conclusions

The supraclinoid portions of the carotid arterial systems from 239 women whose ages ranged from 30 to 89 years were examined to determine the degrees of narrowing caused by cerebral atherosclerosis. Cases chosen for study were from a series previously reported in which the degree of coronary atherosclerosis was determined. The following observations were made:

1. The mean of the maximal grades of atherosclerosis present in 6 cerebral arterial branches of the carotid system steadily increased with age. Progression of atherosclerosis became more rapid after the fourth decade of life and then continued to increase at about the same rate through the ninth decade.

2. In the fourth decade, three fourths of the patients were free of more than minimal cerebral atherosclerosis. In the ninth decade only 3 per cent remained free of cerebral atherosclerosis. Severe cerebral atherosclerosis was nonexistent in the fourth decade and occurred in less than a tenth of the cases in the fifth, sixth, and seventh decades. In the eighth and ninth decades it occurred in one third of the cases.

3. The middle cerebral arteries had a slightly greater degree of atherosclerosis than did the anterior cerebral arteries.

4. Coronary arteries tended to develop atherosclerosis earlier than did cerebral arteries. A wide degree of variability often existed between the severity of atherosclerosis in the coronary arteries and the cerebral arteries in any one case. When the figures from a number of cases were considered, the mean atherosclerosis steadily progressed in severity with age in both vascular systems through the eighth decade. Mean cerebral atherosclerosis also increased through the ninth decade in contrast to mean coronary atherosclerosis, which tended to level off after the eighth decade.

5. Brains in this study having recent or healed cerebral infarcts had a greater degree of atherosclerosis than did brains without infarcts. This difference still existed but was less marked in the ninth decade.

6. Cerebral atherosclerosis was more severe in patients with hypertrophied hearts than in those with nonhypertrophied hearts. After the fourth decade this difference averaged between 10 and 50 per cent.

7. The state of nutrition at the time of death seemed to have little relation to the severity of cerebral atherosclerosis.

Summario in Interlingua

Le portiones supraclinoide del systemas de arterias carotic de 239 feminas de etates de inter 30 e 89 annos esseva examinate pro determinar le grados de restriction causate per atherosclerosis cerebral. Le casos seligite pro le presente studio pertineva a un serie pro le qual le grados de atherosclerosis coronari habeva essite determiate in le curso de un previemente reportate investigation. Le sequente observationes esseva facite.

1. Le valores medie del grados maximal de atherosclerosis trovate in 6 brancas cerebroarterial del systema carotic cresceva uniformemente con le etate del subjectos. Le progression del atherosclerosis se accelerava

post le quarte decennio del vita e continuava subsequentemente accelerar se de modo constante usque al fin del none decennio.

2. In le quarte decennio, tres quartos del patientes esseva libere de plus que minimal grados de atherosclerosis cerebral. In le none decennio, solmente 3 pro cento esseva libere de atherosclerosis cerebral. Sever grados de atherosclerosis cerebral non existeva in le quarte decennio e occurreva in minus que un decimo del casos in le quinte, le sexte, e le septime decennio. In le octave e le none decennio illo occurreva in un tertio del casos.

3. Le arterias medio-cerebral habeva un levemente plus alte grado de atherosclerosis que le arterias antero-cerebral.

4. Le arterias coronari tendeva a devenir atherosclerotic plus tosto que le arterias cerebral. Le casos individual monstrava extense variationes in le relation inter le severitate de atherosclerosis in le arterias coronari e le severitate de atherosclerosis in le arterias cerebral. Quando le valores trovate in un numero de casos esseva combinate, le severitate medie del atherosclerosis acceresceva continuemente con le etate del individuos, tanto in le arterias cerebral como etiam in le arterias coronari. Le valor medie pro atherosclerosis cerebral tendeva a crescer a transverso le none decennio, per contrasto con le valor medie pro atherosclerosis coronari le qual tendeva a formar un plateau post le octave decennio.

5. In iste studio, cerebros con recente o curate infarcimentos cerebral exhibiva plus alte grados de atherosclerosis que cerebros sin infarcimento. Iste differentia persisteva sed esseva minus marcate in le none decennio.

6. Atherosclerosis cerebral esseva plus sever in patientes con hypertrophia cardiac que in patientes con cordes non hypertrophiate. Post le quarte decennio iste differentia habeva un valor medie de inter 10 e 50 pro cento.

7. Le stato de nutrition al tempore del morte pareva monstrar pauc correlation con le severitate del atherosclerosis cerebral.

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Some Evidence for Active Constriction in the Human Pulmonary Vascular Bed

By Dali J. Patel, M.B.B.S., Ph.D., Ramon L. Lange, M.D., and Hans H. Hecht, M.D.

Continuous infusion of norepinephrine in man caused a rise in pulmonary arteriolar resistance as measured by pulmonary artery-pulmonary wedge pressure differences. Since no change in flow occurred during the procedures, the data suggest active constriction of the pulmonary vascular bed under these circumstances.

THE capacity of small pulmonary blood vessels for vasoconstriction remains a controversial subject.[1, 2] Evidence is accumulating which suggests that at least under abnormal circumstances vasoconstriction of the pulmonary vascular bed may occur.[3] The following is a report on changes in pulmonary arteriolar resistance (PAR) during norepinephrine infusion based on simultaneous measurements of blood flow and pressures in the pulmonary vascular system. The pulmonary arteriolar resistance depends on the physical dimensions (geometry) of the vascular bed and on the viscosity of blood (Poiseuille-Hagen equation). If one assumes that the viscosity undergoes no measurable change during administration of norepinephrine, the decisive factor responsible for a change in resistance should be a change in radius of the small vessels. A rise in pulmonary artery pressure alone would tend to dilate vessels passively and to lower the pulmonary arteriolar resistance. An increase in this resistance in the presence of a rise in pulmonary artery pressure constitutes evidence for active vasoconstriction in the pulmonary vascular bed.

Methods

Twenty-one subjects were studied. Venous catheterization of the heart was performed in the usual manner. Cardiac output (Q) was determined by the Fick principle by means of gas analysis. Pressure measurements were made during the Fick determination with a Statham resistance wire transducer, the output of which was fed directly to a D'Arsonval type galvanometer and recorded photographically.[4] Pulmonary artery (PA) and "pulmonary artery wedge" (PA-wedge) positions were selected as 2 points between which the fall in pressure ($\triangle$P) was noted. These pressures were determined in rapid succession or simultaneously by means of no.-6 catheters. The pressures measured at these points were taken to be those proximal and distal to the anatomic or physiologic locus of resistance to flow. Since simultaneous measurements of pressure from the pulmonary artery-wedge and from the left atrium have yielded identical values under many varying conditions, one may assume that the pulmonary artery-wedge pressure affords a reasonably satistory measurement of the postarteriolar pressure. A wedge position was assumed to be present when (a) the catheter could not be advanced farther, and the tip did not move with the cardiac cycle, (b) the pressure contour changed abruptly in the face of an accurately responding and optimally damped catheter—strain gage—galvanometer system, and (c) either no blood could be withdrawn or the blood obtained contained as much or more oxygen than a systemic arterial blood sample.[5] Mean pressure values were obtained by planimetry. The pulmonary arteriolar resistance (PAR) was calculated as

$$PAR = \frac{\triangle P}{Q} = \frac{(PA - PA\text{-wedge}) \text{ pressure}}{\text{cardiac index}} = \frac{\text{mm. Hg} \times \text{min.} \times \text{M.}^2}{\text{liters}}.$$

These units of resistance were chosen for simplicity. In order to minimize the effects of variation in body size on the calculated values, cardiac output was corrected for body surface area (cardiac index). It should be emphasized that the pulmonary arteriolar resistance as measured is unaffected by changes in the volume of the pulmonary vascular bed.

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TABLE 1.—*Influence of Norepinephrine Infusion upon Pressure and Flow*

Patients No.	Age	S.A.	State	H.R. beats/ min.	B.P. mm. Hg	PA*	PA-wedge*	△P mm. Hg	CI†	PAR‡
Normal subjects										
1.	28	1.88	C	75	90	11	3	8	4.3	1.9
			C	65	87	19	(8)	11	4.4	2.5
			NE	60	100	24	(12)	12	4.1	2.9
			NE	36	130	31	(21)	10	2.5	4.0
2.	32	1.69	C	90	95	12	(10)	2	4.2	0.5
			NE	55	126	28	(20)	8	1.9	4.2
3.	30	2.60	C	70	93	16	(9)	7	2.5	2.8
			C	60	93	18	(9)	9	2.4	2.4
			NE	60	125	30	(19)	11	4.1	2.7
			C	80	88	14	(8)	6	2.7	2.2
			NE	55	115	20	(16)	4	2.9	1.4
			C	70	93	15	(9)	6	3.0	2.0
4.	22	1.76	C	75	87	20	(8)	12	4.6	2.6
			C	75	92	19	(9)	10	3.6	2.8
			NE	55	117	30	(17)	13	3.4	3.8
			NE	55	113	30	(16)	14	3.8	3.7
5.	41	1.90	C	65	97	14	(11)	3	2.8	1.1
			C	70	98	14	5	9	3.2	2.8
			NE	50	130	23	12	11	2.9	3.8
			C	75	93	17	(9)	8	2.7	3.0
6.	29	2.19	C	60	97	15	11	4	2.9	1.4
			C	70	97	13	(11)	2	3.2	0.6
			NE	50	133	23	11	12	4.3	2.8
7.	30	1.80	C	58	88	12	(8)	4	3.6	1.1
			C	65	88	12	(8)	4	3.2	1.3
			NE	48	107	16	(14)	2	4.7	0.4
8.	23	1.85	C	75	67	10	(7) +	3	3.8	0.8
			NE	60	80	20	(7) +	13	4.5	2.9
9.	30	1.93	C	62	98	16	(11)	5	2.4	2.1
			C	62	98	16	(11)	5	2.3	2.2
			NE	52	114	24	(16)	8	2.8	2.9
10.	27	2.04	C	88	102	20	(12)	8	2.7	3.0
			NE	58	139	26	(22) +	4	2.7	1.5
11.	33	2.03	C	75	100	20	(12)	8	4.5	1.8
			C	75	99	17	(11)	6	3.5	1.7
			NE	48	140	27	(22) +	5	3.0	1.7
			NE	50	130	26	(21)	5	3.9	1.3

Two milligrams of norepinephrine (Levophed) in 200 ml. of normal saline were given by intravenous drip. The dose was adjusted to give a sustained rise in mean systemic blood pressure of 20 to 40 mm. Hg. In a representative experiment, the infusion was adjusted to a rate of 40 drops a minute (20 μg. of norepinephrine-base).

During the experimental procedure it was nec-

TABLE 1—(*Continued*)

Patients No.	Age	S.A.	State	H.R. beats/ min.	B.P. mm. Hg	PA*	PA-wedge*	△P mm. Hg	CI†	PAR‡
12.	22	1.88	C	60	110	20	(15)	5	4.4	1.1
			C	60	110	20	(15)	5	4.2	1.2
			NE	56	128	35	(20)	15	5.4	2.8
			NE	56	128	35	(20)	15	4.0	3.8
13.	23	1.82	C	72	75	16	14	9	2.9	0.7
			C	70	75	18	14	4	3.3	1.2
			NE	50	107	31	18	13	3.7	3.5
14.	33	1.88	C	70	93	15	12	3	7.5	0.4
			NE	65	110	30	16	14	7.8	1.8
15.	30	1.72	C	70	95	19	12	7	3.8	1.8
			C	65	95	18	(10)	8	4.0	2.0
			NE	50	110	24	14	10	3.9	2.6
			NE	48	112	30	(15)	15	3.7	4.1
16.	31	1.80	C	78	95	13	10	3	3.4	0.9
			NE	55	132	30	18	12	3.6	3.3
17.	26	1.80	C	100	84	—	4	—	3.3	—
			NE	75	110	—	16	—	5.6	—
			NE	90	110	—	10	—	3.9	—
18.	27	1.87	C	60	99	—	10	—	4.0	—
			C	60	99	—	12	—	3.7	—
			NE	46	108	—	19	—	4.0	—
			NE	60	107	—	15	—	4.7	—
			C	60	97	—	14	—	4.3	—
Subjects with abnormal pulmonary vascular bed:										
19. MS pre-op	27	1.74	C	60	68	25	18	7	3.8	1.8
			C	60	68	25	18	7	4.1	1.7
			NE	50	120	37	28	9	3.0	3.0
20. MS post-op	41	1.66	C	60	80	25	12	13	2.5	5.2
			NE	54	100	40	20	20	2.2	9.1
21. Corpulmonale	58	1.52	C	84	79	29	3	26	3.4	7.7
			NE	45	113	35	9	26	2.7	9.6

* mm. Hg
† L./min./M²
‡ $\frac{\text{mm. Hg min.} \times \text{M.}^2}{\text{L.}}$ = (units of resistance)
C Control
NE After norepinephrine infusion

ssary to obtain both wedge pressures and true pulmonary artery blood samples at frequent intervals. In consequence, wedge pressures could not be obtained at all times or in all subjects. In some instances they were estimated from figure 1 by the following procedure: all the 21 points of measured pulmonary artery-wedge pressures from normal subjects, during control and norepinephrine drip, were plotted against corresponding systemic blood pressure measurements. This correlation

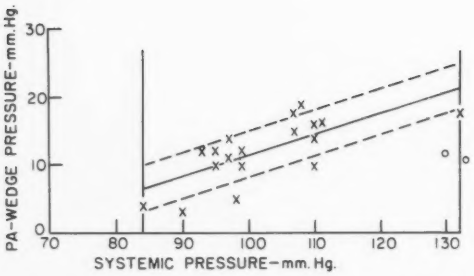

FIG. 1. Regression line for estimation of pulmonary artery wedge pressure from systemic pressure.

was satisfactory ($r = 0.73$). A regression line, therefore, was constructed from these points. This shows that a rise in pulmonary artery-wedge pressures under the circumstances of the experiment was regularly associated with an elevation of systemic pressures in a predictable manner. Missing pulmonary artery-wedge pressures could, therefore, be read off from the graph for the corresponding systemic pressures. This was done within the mean systemic pressure range of 83 to 132 mm. Hg. (The estimated values for wedge pressures are bracketed in table 1. For a systemic pressure beyond this range the limiting values were used (shown with a + in table 1). These data are incorporated here merely to supplement the findings obtained by actual measurements of all pressure values (table 2).

RESULTS AND DISCUSSION

Table 1 gives the basic data obtained in 18 normal subjects and in 3 subjects with a supposedly abnormal pulmonary vascular bed. In table 2 the mean values of pulmonary arteriolar resistance (obtained from measured pulmonary artery-wedge pressure only) before and after norepinephrine administration are shown. Table 3 summarizes the results obtained from statistics of paired data. A significant over-all increase in pulmonary arteriolar resistance was obtained, ($p < .01$). Figure 2 illustrates the rise in pulmonary arteriolar resistance after norepinephrine in one subject (no. 16) in whom the flow, pulmonary artery pressure, and pulmonary artery-wedge pressure were measured simultaneously by means of 2 cardiac catheters. Fowler et al.[2] in similar experiments failed to show a significant rise in pulmonary arteriolar resistance though the total pulmonary

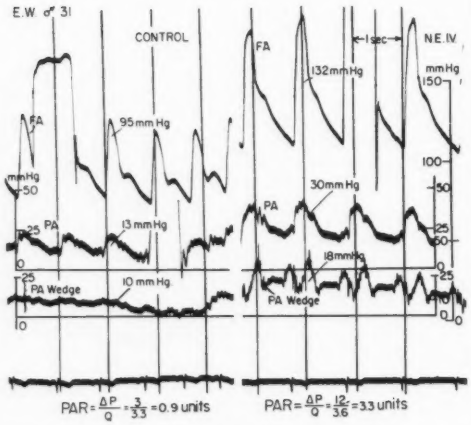

FIG. 2. Increase in pulmonary arteriolar resistance before and after norepinephrine in one patient representing the group of normal subjects.

resistance increased in their experiments. In our series, estimations of the total pulmonary resistance also demonstrated increased values. The significance of these calculations is doubtful, since the second pressure point used in calculating total pulmonary resistance is assumed to be 0, which may not be justified since the norepinephrine infusion caused changes in the systemic circulation as well.

Several factors may have been responsible for the observed changes in pulmonary arteriolar resistance: (1) turbulence may have occurred by an increase in flow and other intravascular alterations that could result in pressure differences in the system; (2) a change in blood viscosity may alter vascular resistance; and (3) active pulmonary arteriolar constriction took place. Inasmuch as flow as measured did not increase following norepinephrine infusion, turbulence is not likely to have been present. In general, the inability, even with high flow rates, to demonstrate a measurable pressure variation in a pulmonary artery system of normal configuration would exclude the possibility that turbulent flow, even if present and not recognized, could be responsible for significant pressure changes. In addition, careful auscultation during the infusion period failed

TABLE 2.—*Rise in Pulmonary Arteriolar Resistance (PAR) following Norepinephrine (NE) Administration: Direct Measurements*

Number	Control PAR	PAR after NE	Difference
ormal subjects			
5.	2.8	3.8	+1.0
6.	1.4	2.8	+1.4
13.	1.0	3.5	+2.5
14.	0.4	1.8	+1.4
15.	1.8	2.6	+0.8
16.	0.9	3.3	+2.4
Mean	1.4	3.0	+1.6 (114% increase)
Subjects with abnormal pulmonary vascular bed			
19.	1.8	3.0	+1.2
20.	5.2	9.1	+3.9
21.	7.7	9.6	+1.9
Mean	4.9	7.2	+2.3 (47% increase)

TABLE 3.—*Statistical Analysis of the Influence of Norepinephrine on the Pulmonary Arteriolar Resistance (PAR)*

Type of subjects	No.	Mean rise in PAR (resistance units)	Standard deviation	Standard error of the mean	p
1. All normal subjects (PAR calculated from measured and from estimated PA-wedge pressures).	16	1.2	1.35	0.34	<0.01
2. Normal subjects (PAR calculated from measured PA-wedge pressure only).	6	1.6	0.71	0.29	<0.01
3. All subjects in whom PAR was calculated from measured PA-wedge pressure.	9	1.8	0.97	0.32	<0.01

to reveal any murmurs in the pulmonary area or elsewhere. It is not likely that the viscosity changed significantly after norepinephrine administration. In several instances, no change was noted in the volume of packed red cells or sedimentation rate, no rouleaux formation was noted on a blood smear, and at constant temperature and pressure head, the control blood and blood with norepinephrine, flowed at an approximately constant rate through a no. 20 needle.

Thus, the third possibility remains as the most likely cause for the changes observed, and it can be concluded that the increase in pulmonary arteriolar resistance noted in our experiments was most likely due to narrowing of the pulmonary vascular bed. This in the presence of increased pulmonary vascular pressure, could only be interpreted as caused by active vasoconstriction.

In 3 patients with diseased pulmonary vascular bed, the mean rise in pulmonary arteriolar resistance was less marked (47 per cent of control) than in normal subjects (114 per cent of control) (table 2). This may well be because an abnormal pulmonary vascular bed may only have a limited capacity to constrict.

The site of the pulmonary vascular constriction during the norepinephrine infusion is speculative but presumably occurs in small pulmonary vessels. Histologic evidence for the presence of smooth muscle in small pulmonary arteries is scanty,[1] but a single helical muscle band winding around a small vessel could cause active vasoconstriction and yet escape detection in histologic cross sections. Observations by one of us[6] in rabbits suggest such a mechanism.

SUMMARY

Eighteen normal subjects and 3 patients with diseased vascular beds were studied. Simultaneous flow and pressure measurements were made during control and intravenous administration of norepinephrine. Enough norepinephrine was given to cause a sustained rise in mean systemic pressure of 20 to 40 mm. Hg. Pulmonary arteriolar resistance was calculated by dividing the pres-

sure difference measured between pulmonary artery to pulmonary artery-wedge by flow. A statistically significant rise in pulmonary arteriolar resistance due to norepinephrine was found in 16 normal subjects ($p < 0.01$: paired data analysis). A decreased response was noted in 3 subjects with diseased pulmonary vascular bed.

The rise in pulmonary arteriolar resistance in the presence of increased pulmonary vascular pressures strongly suggests active constriction of the pulmonary vascular bed.

Summario in Interlingua

Dece-octo subjectos normal e 3 patientes con vasculaturas pathalogic esseva studiate. Mesurationes simultanee de fluxo e pression esseva effectuate sub conditiones de controlo e post le administration de norepinephrina intravenose. Le doses del droga sufficeva a causar prolongate augmentos per 20 a 40 mm. de Hg in le pression systemic medie. Le resistentia pulmono-arteriolar esseva calculate per divider le mesurate differentia inter le pression pulmono-arterial e le cuneate pression pulmono-arterial per le magnitude del fluxo. Statisticamente significative augmentos del resistentia pulmono-arteriolar como effecto de norepinephrina esseva constatate in 16 subjectos normal (p 0,01: analyse de datos appareate). Un reducite responsa esseva notate in 3 subjectos con morbide vasculatura pulmonar.

Le augmento del resistentia pulmono-arteriolar in le presentia de augmentos del pression pulmono-vascular es un forte argumento pro le existentia de constriction active del vasculatura pulmonar.

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The critical sense and sceptical attitude of the Hippocratic school laid the foundation of modern medicine on broad lines, and we owe to it: first, the emancipation of medicine from the shackles of priestcraft and of caste; secondly, the conception of medicine as an art based on accurate observation, and as a science, an integral part of the science of man and of nature; thirdly, the high moral ideals expressed in that 'most memorable of human documents', the Hippocratic oath; and fourthly, the conception and realization of medicine as a profession of a cultivated gentleman.—William Osler. *Aequanimitas and Other Addresses.* Blakiston & Co., Philadelphia, and T. K. Lewis, London, 1904.

The Syndrome of Dextroversion of the Heart

By ROBERT P. GRANT, M.D.

On the basis of 3 personal cases and 119 additional cases collected from the literature the difference between dextroversion and mirror-image dextrocardia is outlined. It is concluded that dextroversion is a part of an exceedingly primitive arrest in development that frequently includes other thoracic and abdominal organs as well as intracardiac structures. The defect is altogether different in embryogenesis and anatomic findings from mirror-image dextrocardia.

THERE are 3 conditions that are characterized by dextrocardia, or right-lying heart. The commonest and most familiar is mirror-image dextrocardia, in which the anterior-posterior relationships of the various parts of the heart are normal but their right-to-left orientation is reversed. It is usually easily recognized because it is practically always associated with some degree of abdominal situs inversus, rarely are there any other cardiac abnormalities, and the electrocardiographic changes it produces are diagnostic, with inverted P, QRS, and T waves in lead I. The second cause of dextrocardia is dextroposition, in which an otherwise normal heart is shifted to the right by some extracardiac factor such as eventration of the left diaphragm, fibrosis of the right lung, etc., and therefore is also usually easily recognized. The third type is dextroversion. It is the least familiar, but perhaps the most important of the 3 from the clinical point of view because it is frequently accompanied by other intracardiac abnormalities, often of a serious nature. Furthermore, the embryogenesis of dextroversion is closely related to the embryogenesis of the cono-truncal region of the heart, and understanding the mechanism of dextroversion sheds light on other congenital malformations.

Dextroversion has been recognized under several different names in the past: "isolated" dextrocardia, incomplete rotation of the heart, dextrotorsion, etc. However, the recent comprehensive studies by Korth and Schmidt[1, 2] have made it clear that it is a distinctive syndrome with broader clinical and embryologic implications than these names imply, justifying the special term dextroversion. In general, dextroversion consists of a rotation of the ventricular part of the heart to the right, as in turning the page of a book, with the atria remaining in normal position. Usually there are transposition of the great vessels and a ventricular septal defect. Since the atria are in normal position, the direction of spread of atrial depolarization is the same as in the normal subject and therefore the P wave in lead I is upright, differentiating it from mirror-image dextrocardia. The QRS and T waves in dextroversion depend upon the type and degree of associated intracardiac malformation. If there is no significant associated abnormality, the mean T vector is often rightward, producing a negative T_1 and the QRS loop is counterclockwise in the frontal plane, producing a Q_1. In the past the negative T_1 has often been attributed to ischemia; but, as shown in figure 1, it is likelier that it is due to rotation of the ventricular electric field on its long axis, for the QRS-T angle is usually a narrow one, as in the normal heart. A more detailed description of the certain aspects of the syndrome will follow the presentation of 3 selected cases, 2 of which were studied by biplane angiocardiography and 1 at postmortem examination.

Case 1. D.D. (Clinical Center #016355): a 2-year-old girl had been cyanotic with episodes of labored breathing since birth. There were no signs of congestive heart failure. The heart was not

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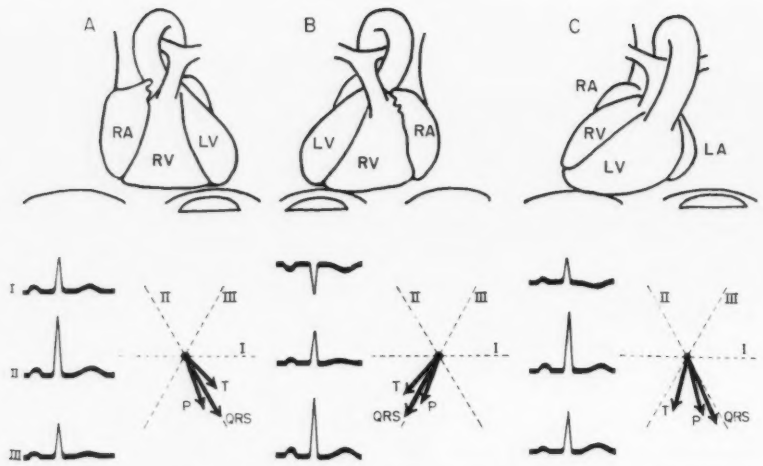

FIG. 1. *A*, the normal heart, *B*, classical mirror-image dextrocardia, *C*, classical dextroversion. The position of the 4 cardiac chambers, the great vessels, and the gastric gas bubble are shown for each. Below, standard limb leads and the frontal plane projections of mean cardiac vectors in the uncomplicated case are shown. Note the difference in cardiac silhouette between mirror-image dextrocardia and dextroversion. In the latter, the apex is blunter, there is a prominent shadow high on the right side due to the right atrium, and the transposed aorta forms a prominent slow curve on the upper left side of the silhouette in the typical case.

enlarged, lay to the right, and a high pitched grade III systolic murmur was noted over the entire precordium, maximal in the second interspace to the right of the sternum. The abdominal organs appeared to be normally placed. The hematocrit value was 83 per cent (Wintrobe). In the electrocardiogram the P waves were upright in all 3 limb leads, the mean QRS vector was directed superiorly and to the right with QS deflections in the 3 standard limb leads and conventional V_3 to V_6. The mean T vector was directed inferiorly. On cardiac catheterization the catheter was passed through the venous right-lying atrium into both an arterial and a venous ventricle. The pressure in the venous ventricle was slightly higher than in the arterial ventricle; neither the aorta nor pulmonary artery could be entered. On selective angiocardiography with the catheter in one of the ventricles (fig. 2) there was immediate filling of both ventricles, with a small jet of radiopaque medium extending into the pulmonary artery (first film). At ¾ second the pulmonary artery was well filled, showing narrowing proximally, and the contrast material could be seen regurgitating slightly into both atria. At 1¼ seconds ventricular diastole had occurred, with marked reduction in the degree of opacification of the right ventricle and a central area of translucency in the left ventricular shadow due to the entrance of nonopacified blood from the atria. The difference in opacification between the right and left ventricles at this stage demarcated the ventricular septum, which was more or less parallel with the horizontal or transverse plane of the body. At 1¾ seconds the ventricles had contracted and the aorta was opacified for the first time, showing it to lie anteriorly to the pulmonary artery. In later films (not shown) the pulmonary veins were opacified and could be seen draining to the lower left region of the cardiac silhouette, indicating that the left atrium was normally placed. The gastric bubble appeared normally placed. The diagnosis was dextroversion, with atrial and ventricular septal defects and transposition of the great vessels.

Case 2. J.W. (Clinical Center #017046), a 5-month-old girl, had been cyanotic and slightly short of breath since birth. There were no murmurs or signs of decompensation. Hemoglobin was 15 Gm. per cent, with many Howell-Jolly bodies and a few spherocytes in the peripheral blood smear. Her electrocardiogram showed upright P waves in the 3 standard limb leads; the mean QRS axis was leftward and inferior in direction with qR deflections on leads I and II and principally upright QRS complexes of qR type from V_2 to V_4. During her episodes of dyspnea the mean QRS vector gradually but transiently rotated to marked left axis deviation without pro-

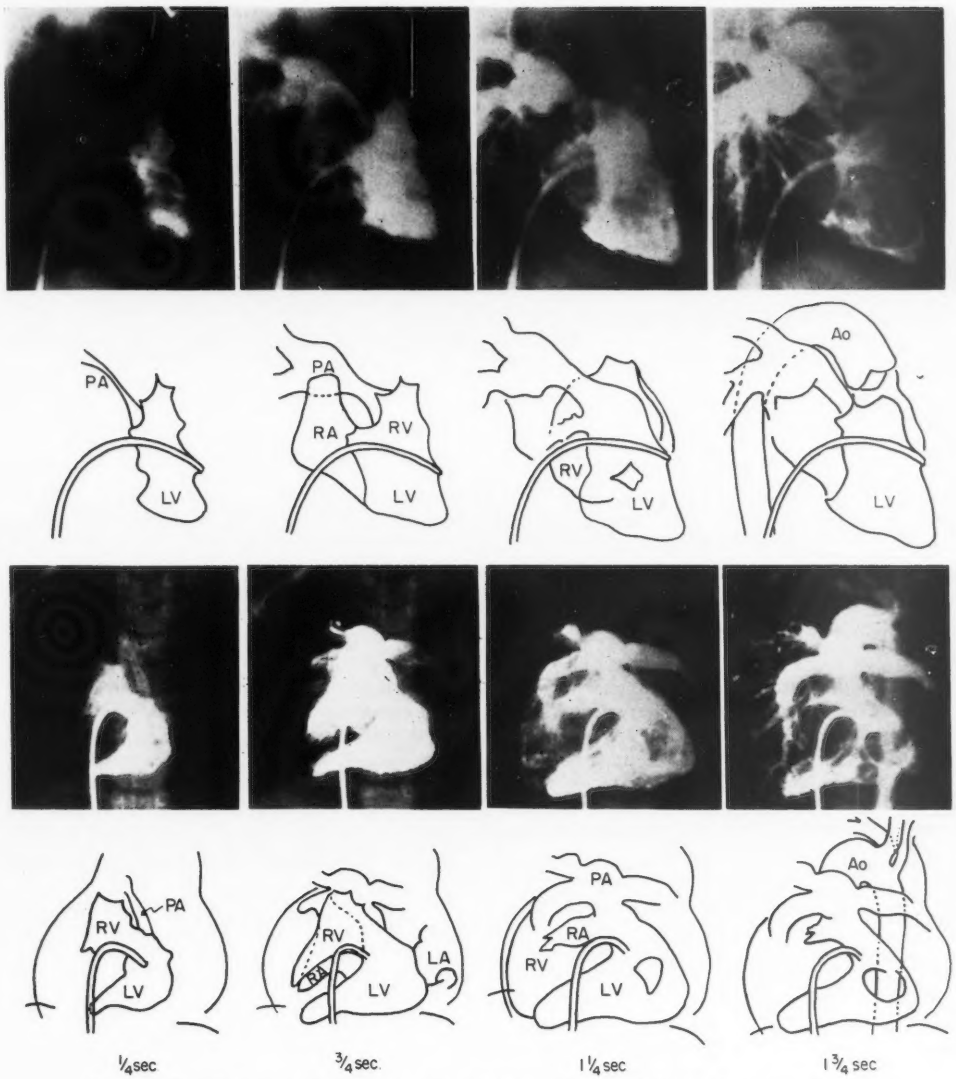

FIG. 2. Simultaneous lateral (*top*) and anterior-posterior (*bottom*) biplane angiocardiogram in case 1. The opacification for each film is diagrammed below it, and the time of the film after injection of the contrast material is indicated at the bottom of the figure. The position of the catheter through which the contrast material was injected is shown. Both ventricles fill in the first film, demonstrating the presence of a ventricular septal defect. In the second and third anterior-posterior films, the plane separating the right and left ventricles is well defined, indicating that the ventricular septum lay more or less perpendicular to the frontal plane of the body, with the right ventricle superior to the left ventricle. In the fourth lateral film it can be seen that the aorta is anterior to the pulmonary artery, demonstrating the presence of transposition of the great vessels; usually the aorta has a more leftward position than in this case. In still later films (not shown) the passage of contrast material from the pulmonary veins into a chamber to the left of the left ventricle could be seen, indicating that the left atrium was normally located.

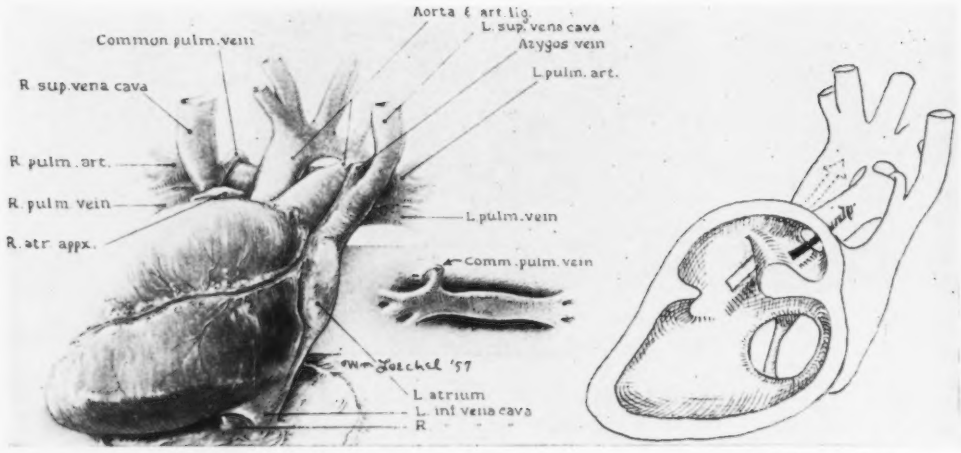

FIG. 3. The heart in case 2, viewed frontally as it lay in the chest. Right, schema of the internal structure of the heart from the same view. The interventricular septum, represented by only a shelf, is perpendicular to the frontal plane of the body; the right ventricular portion of the heart lies superiorly to the left ventricle. The muscular ridge at the proximal end of the tissues separating aorta and pulmonary artery is interpreted to be the crista supraventricularis; it is more or less parallel with the frontal plane of the body, which is its normal anterior-posterior position, and in this heart it is at right angles to the position of the ventricular septum.

longation of the QRS interval. The mean T vector was directed rightward, superiorly, and slightly anteriorly. Shortly after admission she began to have episodes of sudden limpness with grunting respirations and intensified cyanosis. She died during one of these episodes before diagnostic studies could be undertaken.

At autopsy (performed by Dr. Louis Thomas) abnormalities of thoracic and abdominal organs were found. The heart lay principally rightward with the posterior sulcus (which normally faces the diaphragm and contains the descending branch of the right coronary artery) facing anteriorly, indicating that the right ventricle was superior to the left (fig. 3). The heart was somewhat enlarged, measuring 5.5 cm. in its long axis, with right and left ventricular walls 5 mm. thick. There were 4 venae cavae. The 2 superior venae cavae lay on each side of the mediastinum, one entering the right, the other the left side of a single large atrial chamber, which had only a few strands of atrial septal tissue. These strands indicated that the septum was more or less parallel with the frontal plane of the body, its normal position. The identification of right versus left atrial structures was not possible, but in view of the normally directed P vector in the electrocardiogram, the sinus node lay rightward, indicating that the atria were normally placed. One inferior vena cava drained solely the left lobe of the liver and entered the left side of the atrial chamber. The other inferior vena cava entered into the right side of the common atrium, draining the right lobe of the liver, the kidneys, adrenal glands, pancreas, and lower extremities with only minor variations from the normal in its architecture. The ventricular portion of the heart consisted of essentially a single chamber, with a rudimentary ledge at its lateral and inferior border suggesting a ventricular septum. A single A-V orifice connected the common atrium and common ventricle. It had 3 leaflets that were incompletely developed and separated. There was a prominent muscular ridge in the outflow region of the common ventricle that separated the aortic and pulmonary orifices. Both orifices had 3 well-formed cusps. The coronary artery orifices were normally placed, and the coronary arteries had a normal distribution over the ventricular myocardium. The pulmonary artery was anterior and to the left of the root of the aorta, and was 1.4 cm. in diameter while the aorta was 1.0 cm. A completely obliterated ligamentum arteriosus connected the 2 vessels. The branchings and distributions of the pulmonary artery and aorta were normal. The pulmonary veins from both lungs joined to form a common pulmonary vein that entered the right superior vena cava. The right lung had 3 lobes, and a prominent demarcation of the lingular part of the left lung gave it 3 lobes also. In the abdomen, the left lobe of the liver was larger than the right lobe and the gallbladder was attached to the left-

FIG. 4. Angiocardiogram of case 3. The anterior-posterior view prior to injection of contrast material is shown on the left, illustrating the rightward position of the heart. Middle, a film selected from the angiocardiographic series to show the positions of the right ventricle and right atrium. Right, diagram of the opacification in this film. Later films outlined the aorta and pulmonary artery, shown by dotted lines in the diagram. The plane separating right from left ventricle has a more sagittal position in this case than in case 1. There was no transposition of the great vessels. Note the gastric gas bubble under the left leaf of the diaphragm. The catheter through which the contrast material was injected can also be seen.

lying lobe. The spleen was absent. The stomach lay in the left upper quadrant, its antral region deviated by a torsion in the position of the duodenum that was folded by its attachment to the left-lying gallbladder. The tail of the pancreas extended leftward but was not retroperitoneal and lay free in the abdomen. Both the lesser and greater omenta were incompletely developed, as were also the mesenteries of the small and large bowels. Counterclockwise rotation of the bowel had failed to take place, and the ileocecal valve, cecum and vermiform appendix lay in the left upper quadrant. The large bowel from the sigmoid to the rectum was normal in location. The portal venous system was normal. The diagnoses were dextroversion of the heart with atrial and ventricular septal defects, common pulmonary vein, single atrioventricular orifice, persistent right superior and inferior venae cavae, asplenia, partial situs inversus of the liver and gallbladder and incomplete development of other abdominal and thoracic organs.

Case 3. S.C. (Clinical Center #019515), an 8-year-old girl, was first noted to have a murmur at 3 months of age. Cyanosis had not been noted, but she complained of fatigability on exertion. On examination the arterial blood pressure was 0/60; there was no cyanosis, clubbing, or evidence of congestive heart failure. The maximal cardiac impulse was noted to be in the right fifth interspace, but abdominal organs appeared to be normally placed. An extremely loud, high-pitched diastolic murmur was noted along the left sternal border. Hemoglobin was 16 Gm. per cent. The electrocardiogram disclosed upright P waves in the standard limb leads, the mean QRS axis was

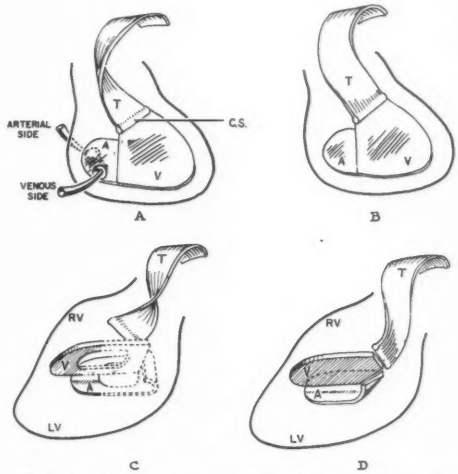

FIG. 5. Topologic schemata of the surfaces separating arterial from venous parts of the heart; *A*, the normal heart, *B*, transposition of the great vessels in a normally placed heart, *C*, dextroversion without transposition (drawn from case 2; the atrial and ventricular septa were not completely developed in this heart, the undeveloped portions are represented by dotted lines), *D*, dextroversion with transposition of the great vessels. *T*, the plane tangential to both the pulmonary artery and the aorta; *V*, ventricular septum; *A*, atrial septum; *C.S.*, crista supraventricularis.

directed rightward and inferiorly, with a qrS contour in lead I; the mean T vector was directed horizontally rightward, and the conventional pre-

cordial leads all showed RS contours with inverted T waves as far as V_6. On right heart catheterization the pulmonary artery wedge pressure was normal, pulmonary artery pressure was 110/60, right ventricular pressure was 110/5, and right atrial pressure was normal. The arterial blood was 81 per cent saturated and both right-to-left and left-to-right shunts were detected at the level of the pulmonary artery. On angiocardiography (fig. 4) the pulmonary artery and aorta filled simultaneously with the proximal part of the aorta poorly visualized and the pulmonary artery extremely large in size. There was no evidence of transposition of the great vessels, and the aortic arch was left-sided. The atria were normally placed, but the right ventricle lay to the right of the left ventricle with the interventricular septum parallel with the sagittal plane of the body (fig. 5). The gastric bubble was normal in location. The diagnosis was mesoversion of the heart with patent ductus arteriosus. In view of the pulmonary hypertension and evidence of reversed flow through the ductus, surgery was postponed.

Discussion

One hundred and nineteen cases of dextroversion have been reported in the literature, proved either by electrocardiogram or autopsy.* The electrocardiogram is diagnostic of this syndrome, for in the presence of a congenitally right-lying heart an upright P wave in lead I is, with rare exceptions,[15, 19, 22] indicative of dextroversion. An analysis of the 119 cases discloses a number of features of this syndrome that have not been widely appreciated in the past.

It is often believed that a basic difference between mirror-image dextrocardia and dextroversion is that the former is associated with situs inversus while the latter is not. In fact, it is because of this notion that dextroversion has frequently been called "isolated dextrocardia" in the past. However, while the first part of this statement is relatively accurate (among more than a thousand cases of mirror-image dextrocardia in the literature, Korth and Schmidt could find only 12 that did not have situs inversus, and only 1 of these was studied at autopsy,[1, 23–25]) the second part is not. A number of cases of well-authenticated dextroversion have been reported in which other thoracic and abdominal organs were abnormal either in structure or location, often taking a form that superficially resembled situs inversus. Among the 69 cases of dextroversion in which autopsy data are adequate, at least 16 had some degree of abdominal heterotaxy, including case 2 of the present report. However, there tends to be a basic difference between situs inversus and the heterotaxy seen with dextroversion. In situs inversus the viscera are inverted but, with few exceptions,[24, 26–28] they are otherwise normal and fully developed. On the other hand in dextroversion with abdominal heterotaxy, the involved abdominal organs are nearly always abnormal in form or structure. The abnormality takes a form that is perhaps best described as an embryologic arrest prior to the development of body asymmetry, for the viscera tend to be abnormally symmetric in form and primitive in structure. For example, in the typical case of dextroversion with advanced abdominal heterotaxy, the liver is symmetric with both lobes equal in size, the gallbladder is often central, the duodenum may be either central or nonrotated, the stomach may be central and embedded in the substance of the liver or it may have primitive mesenteric attachments permitting it to lie anywhere in the abdomen, the mesentery of the bowel is often underdeveloped with many different bowel arrangements possible, the pancreas may be a central, unorganized tissue mass, both lungs will be tri-lobed, etc. The heart in dextroversion often best illustrates this arrest at a stage when the body has a simple, symmetric form, for it may show many of the features of the "single heart tube." For example, of the 16 cases of dextroversion with abdominal heterotaxy reported in the literature, 8 had cor biloculare and 5 of these had the combination of a single pulmonary vein, single atrium, single atrioventricular ring, single ventricle, and single outflow organ (truncus arteriosus).[29–35]

A curious anomaly often associated with dextroversion, and one which further empha-

*Korth and Schmidt[1, 2] listed 97; an additional 19 were found in the literature,[3–21] and 3 cases are in the present report.

s zes the difference between dextroversion and
1 irror-image dextrocardia with situs inversus,
i congenital absence of the spleen, a subject
t iat has recently been reviewed by Ivemark[36]
a id Putscher and Manion.[37] Ten of the 69
a itopsied cases of dextroversion (including
(ise 2 of the present report) had asplenia,
v hile among hundreds of cases of situs in-
v ersus totalis reported in the literature, only
7 had asplenia and in this case the diagnosis
v as made during surgical exploration and
1 ot at autopsy.[38] Nearly half of the 107
(ases of asplenia reported in the literature
l ad right-lying hearts, and although the data
a re incomplete in many of them, most if not
a ll were instances of dextroversion. Further-
m ore, among all cases of asplenia 90 per cent
had associated intracardiac anomalies, usu-
a lly cono-truncal abnormalities; this is the
same incidence of cono-truncal deformity
seen in dextroversion, while in mirror-image
dextrocardia additional intracardiac anoma-
lies are exceedingly uncommon. Finally, the
abdominal heterotaxy that usually accompa-
nies asplenia more closely resembles that seen
with dextroversion (i.e., symmetric hetero-
taxy) than it does situs inversus. Ivemark
explained the association of asplenia, abdom-
inal heterotaxy, and cono-truncal malforma-
tion by ascribing it to an arrest of develop-
ment at the stage when the body first searches
out its normal asymmetry, and he points out
that the splenic bud appears and cono-truncal
differentiation takes place at the same fetal
date. Putscher and Manion suggested that
asplenia and heterotaxy may be due to sup-
pression or inhibition of structures that are
asymmetric by their left-sidedness; however
this would not account for the high incidence
of cono-truncal abnormalities in these cases.

The degree of developmental arrest in the
extroversion syndrome varies from case to
ase and from organ to organ in individual
ases. In the heart, for example, certain car-
iac metameres may be arrested while adja-
ent ones develop normally. This is illus-
rated by case 2 of this report where, with
most of the heart arrested at the "single
heart tube" stage (bilateral superior and in-
ferior venae cavae, single atrium, single atri-
oventricular ring, single ventricle, single
common pulmonary vein), the great vessels
were completely differentiated without even
transposition. And there are cases at the
other end of the spectrum, with only a single
feature of the dextroversion syndrome pres-
ent. For example, Korth and Schmidt found
in the literature 6 cases of dextroversion in
which the rightward rotation of the ventricu-
lar part of the heart was the only abnormality
found at autopsy, with no septal defects,
transposition, or abdominal heterotaxy.[1]
When the abnormality is limited in its exten-
siveness, as in these cases, it is clinically be-
nign. Of the 119 cases of proved dextrocar-
dia in the literature, 50 were adults and liv-
ing at the time they were reported. Although
other abnormalities were identified in many
of these cases by clinical or x-ray examination,
the abnormalities were not marked enough to
interfere seriously with cardiac function.

One of the commonest associated intracar-
diac abnormalities in dextroversion is transpo-
sition of the great vessels. Of 59 cases in
which the position of the great vessels was
described either from autopsy or angiocardi-
ography, 5 had truncus arteriosus, and 44 had
transposition of the great vessels. Thus 80
per cent had some form of outflow abnormal-
ity. The transposition is somewhat different
from that seen when the heart is normally
placed, for in dextroversion the aorta lies to
the left of the pulmonary artery and only
slightly anterior to it, while in transposition
with a normally placed heart the aorta is usu-
ally directly anterior to the pulmonary ar-
tery. Thus, the roentgenogram of the heart in
dextroversion shows a wide base if transpo-
sition is present, with the aorta often forming
a prominent, long left margin of the cardiac
silhouette as shown in figure 1. Since the
great vessels lie side by side in this form of
transposition, one might wonder if they are
not simply "uncoiled" by the abnormal
rightward position of the heart. However,
turning the normally placed heart to the right
would tighten the coil of the great vessels, not
uncoil them. To uncoil the great vessels, the

ventricular part of the heart must rotate markedly leftward, a phenomenon that Shaner has reported in the pig embryo and possibly in 1 human fetus.[39] The transposition of dextroversion is nearly always accompanied by a ventricular septal defect. Of 55 cases of dextroversion with adequate autopsy data, 44 had ventricular septal defects. There is only a single case of dextroversion in the literature with transposition but no ventricular septal defect.[40]

This means that a high percentage of cases of dextroversion have one or more associated intracardiac anomalies, (90 per cent of autopsied cases). This is in striking contrast with mirror-image dextrocardia. Among more than a thousand cases of mirror-image dextrocardia with situs inversus in the literature only 5 cases have been found in which additional intracardiac anomalies were or may have been present,[22, 41–43] an incidence not greatly different from that of the population at large. This difference between the 2 syndromes emphasizes the fact that they must be due to quite different embryologic defects. It also leads to the useful clinical aphorism that if, in a patient with a right-lying heart, there is also cyanosis or an abnormal cardiac murmur, the diagnosis is probably dextroversion and not mirror-image dextrocardia regardless of the position of the abdominal organs. The variety of intracardiac and extracardiac abnormalities that may be associated with dextroversion of the heart warrant treating it as a "syndrome" of which the right-lying heart is only a part and perhaps not always present. For example, among Ivemark's 69 cases of asplenia, abdominal heterotaxy, and conotruncal deformity, 46 had no dextroversion. Although precise data are not available, clinical experience also indicates that dextroversion is uncommon among all cases of conotruncal deformity.

The most striking positional anomaly in dextroversion is the rightward location of the ventricular part of the heart. There are 2 reasons for believing that this is due to an arrest at the stage of cardiac development when the ventricular loop normally has a rightward position[44, 45] and is not due to either abnormal inversion or torsion of the heart. In the first place the ventricles are the only part of the heart to have the abnormal position. If it were due to inversion one would expect the atria or the great vessels would also occasionally be inverted. However, there are no cases of dextroversion so far reported in whom the atrial bodies were also abnormal in position; and the arch of the aorta is left-sided in the majority of cases of dextroversion, whether or not transposition is present.[1] (Most students do not consider transposition of the great vessels to be due to inversion, if by inversion one means a translocation resulting from a disturbance of factors that determine body laterality, as in situs inversus; generally, transposition is considered due to a local disturbance in either the rate or magnitude of the spiralling of the truncal septum as it descends.[44, 45]) In the second place, there are in the literature 13 cases in which both atrial appendages lay to the left of the aorta but with normally placed atrial bodies, and at least 8 of these had some degree of dextroversion.[12, 18, 46–52]) Clearly, in these cases the anomalous location of the right atrial appendage must have been due to delay or failure of the bulbus to migrate to the left, and in the cases with dextroversion this failure evidently included the entire ventricular loop.

The particular position of the ventricles in dextroversion requires comment. While it may be graphic to describe the ventricles as "turned to the right as in turning the page of a book," this is not completely accurate. As can be seen from the schema in figure 5, the anatomic drawing in figure 3, and the angiocardiogram in figure 2, the right ventricle lies superiorly to the left ventricle, and the interventricular septum is at right angles to the frontal plane of the body while normally it is parallel with the frontal plane. Thus the ventricular part of the heart is not only rotated to the right but is also rotated on its long axis. For a normally placed heart to take this position it may be swung rightward in either the frontal plane (like a pen-

ılum) or in the horizontal plane (like turn-
g the page of a book). The difference is of
me importance because it is also necessary
rotate the ventricular heart on its long axis
simulate dextroversion completely, and for
e former the supplemental rotation of the
ntricles is 90 degrees in a counterclockwise
rection while for the latter it is 90 degrees
a clockwise direction as viewed from the
pex. This is, of course, an artificial way to
ok at dextroversion. Rather one should ask
hat is the embryologic positional shift that
ils to take place, is it a leftward swing in
he frontal plane (pendular) or a leftward
wing in the horizontal plane (page turning)?
Perhaps this is answered by the angiocardio-
gram of case 3 (fig. 4), for this is an example
of mesoversion, with the heart less markedly
rightward than in dextroversion. It can be
seen that the ventricular septum lies in the
sagittal plane of the body, with the right ven-
tricle to the right and the left ventricle to the
left. If this heart is representative of the
mid-position between dextroversion and the
normally placed heart, then the ventricular
loop comes to lie in the left chest by swinging
about 120 degrees as a pendulum in the fron-
tal plane, and the long axis rotation that
brings the right ventricle to its normal posi-
tion anterior to the left ventricle is a clock-
wise rotation of 90 degrees. Evidently this
latter type of rotation occurs late in the course
of the leftward swing of the ventricular heart
for, in case 3 at least, it has not yet taken
place.

It was pointed out earlier that when the
aorta and pulmonary artery are transposed
in dextroversion they have a somewhat dif-
ferent location than when they are transposed
in the normally placed heart. Doerr[53] ex-
plained this difference by suggesting that in
dextroversion there is an inversion of the bul-
bus cordis in addition to transposition. How-
ever, when the heart of dextroversion is
studied topologically it is found not necessary
to postulate the additional anomaly. In fig-
ure 5 are shown the positional relationships
between the various parts of the normal heart
and the dextroverted heart, with and without
transposition. The positions have been sche-
matized by plotting 3-dimensionally the sur-
faces that separate the right and left sides of
the heart. The surface between the atria is
defined by the atrial septum, that between the
ventricles by the ventricular septum, and that
between the aorta and the pulmonary artery
by the plane tangential to both. It can be
seen from the diagrams that the peculiarity
of the transposition seen in dextroversion is
due to the fact that the rightward position of
the ventricles is simply communicated to the
transposed vessels. For example, if the trunc-
al surface in *D* is swung as a pendulum to the
left it will have the same spatial position as
in transposition in the normally placed heart,
B, and there is no evidence of inversion of the
bulbar region. In contrast with this, in *C* is
shown the schema of the cardiac surfaces in
case 2. When the truncal surface in this case
is swung leftward as a pendulum, it will have
the same spatial position as in the normal
heart, *A*. In other words there is no transpo-
sition in this case, and the normally related
great vessels are simply deviated to the right
by the rightward position of the ventricles.
Note that in *C* while the crista supraventricu-
laris has a normal spatial location, as a result
of the ventricular dextroversion it is at right
angles to the ventricular septum. This re-
sulted in a much severer degree of deformity
from a functional point of view than if trans-
position had taken place. Perhaps, then, the
high incidence of transposition in cases of
dextroversion is simply due to the fact that
normal descent of the truncal septum in a
heart with dextroversion often results in a
deformity that is incompatible with survival
beyond earliest fetal stages and therefore
rarely comes to the attention of either the
clinician or the pathologist. In any case, it is
likely that case 2 survived as long as she did
only because of the presence of large ventricu-
lar and atrial septal defects and a single atri-
oventricular orifice, permitting oxygenated
blood to reach the systemic circuit.

Summary and Conclusions

Three cases of dextroversion and an anal-

ysis of an additional 116 cases collected from the literature are presented. There are 3 major differences between dextroversion and mirror-image dextrocardia. 1. In dextroversion the atria have a normal position but the ventricular heart lies rightward, as if swung like a pendulum through an arc of 120 degrees in the frontal plane from its normal position; there is also a 90 degree counterclockwise rotation of the ventricular heart on its long axis, with the right ventricle lying superiorly to the left ventricle. In contrast with this, in mirror-image dextrocardia all cardiac structures are rightward mirror-images of the normal heart. 2. The vast majority of cases of dextroversion (90 per cent of autopsied cases) have additional intracardiac malformations, usually of the cono-truncal region, while in mirror-image dextrocardia additional intracardiac anomalies are probably no more frequent than in the population at large. 3. An abdominal heterotaxy is often present in dextroversion, which is different from the situs inversus that accompanies mirror-image dextrocardia: instead of inversion of abdominal organs there is a tendency for abdominal structures to be primitive and bilaterally symmetric, frequently with congenital absence of the spleen.

It is suggested that dextroversion is a part of a potentially multiorgan developmental defect that takes place at a very early fetal stage when the body first begins to search out its normal asymmetry, when cardiac septation and cono-truncal differentiation start, when the splenic bud first appears, and when the ventricular loop is normally predominantly rightward in location. Depending upon the intensity and distribution of the abnormality a wide variety of intracardiac and extracardiac anomalies and combination of anomalies may result. Dextroversion of the heart is perhaps only one part of this syndrome.

Transposition of the great vessels is present in over 80 per cent of cases of dextroversion. Indirect evidence is offered which suggests that the high incidence of transposition may partly be due to the fact that, in the presence of dextroversion, a normal descent of the truncal septum often produces a severer functional abnormality than does transposition and these cases do not usually survive earliest fetal stages.

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Summario in Interlingua

Es presentate 3 casos de dextroversion del corde e un analyse de 116 casos additional colligite ab le litteratura. Il ha 3 differentias principal inter dextroversion del corde e dextrocardia specular. (1) In dextroversion le atrios occupa un position normal, durante que le corde ventricular es displaciate verso le dextera, como si—in le maniera de un pendulo—illo habeva essite movite a transverso un arco de 120 grados in le plano frontal foras de su position normal. Il ha etiam un rotation sinistrorse de 90 grados circa le axe longe del corde ventricular, e le ventriculo dextere occupa un sito superior al ventriculo sinistre. Per contrasto con isto, in dextrocardia specular, omne le structuras cardiac es dextrorse correspondentias specular del corde normal. (2) In le grande majoritate del casos de dextroversion del corde (90 pro cento secundo le necropsias reportate), il ha additionalmente malformationes intracardiac, usualmente in le region cono-truncal, durante que anomalias intracardiac in subjectos con dextrocardia specular es probabilemente non plus frequente que in le population general. (3) Un heterotaxia abdominal es frequentemente incontrate in casos de dextroversion del corde, que differe ab le sito inverse associate con dextrocardia specular. In loco de inversion del organos abdominal, il ha le tendentia que le structuras abdominal remane primitive e es bilateralmente symmetric, frequentemente con absentia congenite del splen.

Es presentate le these que dextroversion es possibilemente un parte de un potentialmente extense defecto disveloppamental que occurre multo precocemente in le vita fetal, quando le organismo comencia su "tentativas de asymmetria," quando le septation cardiac e le differentiation cono-truncal se initia, quando le button splenic se manifesta, e quando le ansa ventricular occupa normalmente un loco predominantemente dextrorse. In dependentia del intensitate e del distribution del defectos disveloppamental, un grande varietate de anomalias intra- e extra-cardiac e de combinationes de tal anomalias pote resultar. Dextroversion del corde es forsan solmente un parte de iste syndrome.

Transposition del vasos major es presente in plus que 80 pro cento del casos de dextroversion. Es presentate indicios indirecte que supporta le these que le alte incidentia de transposition del vasos majores in parte causate per le facto que in le presentia de dextroversion un descendita normal del septo truncal produce frequentemente un anormalitate functional que es plus sever que illo producite per transposition, e in caso de un descendita normal del septo truncal le feto non supervive usualmente al prim stadios de su disveloppamento.

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For true Philosophers, who are perfectly in love with truth and wisdom, never find themselves so wise, or full of wisdom, or so abundantly satisfied in their own knowledge, but that they give place to truth whensoever, or from whosoever it comes.—William Harvey. *De Motu Cordis*, 1628.

Serum Glutamic Oxaloacetic Transaminase in Dissecting Aneurysm of the Thoracic Aorta

By JOHN B. TREDWAY, M.D., AND EDWARD E. KEMBLE, M.D.

The behavior of serum glutamic oxaloacetic transaminase level in cases of dissecting aneurysm of the thoracic aorta is reported. Certain clinical and laboratory observations suggest that intrapericardial hemorrhage is the responsible factor when the titer of serum glutamic oxaloacetic transaminase is elevated.

FOR obvious reasons, separation of the entities of myocardial infarction and dissecting aneurysm of the thoracic aorta has often presented a difficult and perplexing problem in clinical medicine. With the advent of serum glutamic oxaloacetic transaminase (SGOT) determination as a diagnostic measure in the diagnosis of myocardial infarction, it has been suggested[1] that this procedure may be of help in differentiating the 2 conditions.

Review of the medical literature to date yields mention of SGOT activity in only 1 case of dissecting aneurysm of the aorta[2] with a single normal value of 18 units. It is the purpose of this report to present 3 cases of dissecting aneurysm of the thoracic aorta, 2 of which showed elevation of serum glutamic oxaloacetic transaminase activity during their clinical course and a third that did not, along with certain observations as to the possible mechanism of the elevated SGOT activity. Determination of SGOT activity was performed by the method of Cabaud, Wroblewski, and Wroblewski.[3]

CASE REPORTS

Case 1. A 71-year-old white physician was admitted to the hospital on May 20, 1956. He had noted severe pain in the substernal region, in the throat, and over the sacral area on the day before admission after treating some people who were badly hurt in an automobile accident. He did some lifting at the time, but returned to his office and worked until 10:00 p.m. During the night the chest pain became sufficiently severe to require meperidine (Demerol) and was made worse by inspiration. There was no sweating or vomiting and the pain persisted until the next day, when he was admitted to the hospital.

He stated that he had experienced some exertional dyspnea for several years and had had systolic hypertension of approximately 200 mm. Hg for the past 15 years.

On physical examination the blood pressure was 170/90 and the pulse was 90 and regular. The heart tones were of fair quality and there were no murmurs. A few fine rales were heard at the right base and some tenderness was noted in the epigastrium on palpation. No abdominal masses were noted. The hemoglobin was 15.3 Gm. per cent, the leukocyte count 14,400, with 57 per cent polymorphonuclear neutrophils, the hematocrit value was 43 per cent and the sedimentation rate was 38 mm. per hour (Westergren). The blood sugar was 102 mg. per cent, the blood urea nitrogen was 18 mg. per cent, and the prothrombin time was 57 per cent of normal. Serum glutamic oxaloacetic transaminase determinations were 115 units on May 20 (approximately 18 hours after onset of pain), 82 units on May 22, 40 units on May 23, and 17 units on May 24. An x-ray of the chest on May 21 showed the heart to be moderately enlarged, with some prominence of the left ventricle. There was no evidence of a double contour of the aorta and no sign of fluid in the pleural cavity. An electrocardiogram on May 21 showed elevated S-T segments throughout the limb and precordial leads, suggestive of acute pericarditis. A second electrocardiogram 4 days later showed that the S-T segments had, for the most part, returned to the isoelectric level.

The patient was not given anticoagulants because the electrocardiographic changes suggested pericarditis. An inconstant murmur was heard over the precordium and at one time a scratchy pericardial friction rub was detected. The patient was comfortable, had no recurrence of precordial pain, and seemed to be convalescing well, when he suddenly died on May 28.

At autopsy the pericardial sac was greatly distended with blood. The pleural spaces were not remarkable and the remainder of the thoracic

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viscera were normal. Some dilatation of the aorta was noted, and a rent was found in its intimal surface approximately 2 cm. above the orifice of the aortic valve. This was associated with a split in the aortic wall, which extended up to the arch. There was also a small rent in the adventitia about 1 cm. above the intimal defect, and around it was a considerable amount of blue discoloration. The adventitial tear was located below the pericardial reflection, so that it was the source of the hemopericardium. The coronary ostia were patent and free from dissection and the coronary arteries showed severe and extensive arteriosclerotic thickening. The remainder of the aorta revealed widespread arteriosclerosis, which was most conspicuous in the abdominal portion. The liver weighed 1,300 Gm. and showed a smooth capsule and passive congestion. Microscopic examination of the myocardium failed to reveal any evidence of infarction; although the lumina of the coronary arteries were narrowed, no thrombus formation within the vessels was noted. Microscopic examination of the liver revealed only terminal passive congestion.

Case 2. A 67-year-old white woman was admitted to the hospital January 2, 1957, because of precordial pain. Crushing, nonradiating anterior chest pain began suddenly about 1 hour prior to admission to the hospital. There was no previous history of any significant illness or disability. Examination on admission showed a semistuporous, desperately ill, cyanotic woman with a blood pressure of 90/60, apical heart rate of 120, distant heart sounds, and no murmurs or friction rub. The blood sugar on admission was 304 mg. per cent and 4 hours later it was 388 mg. per cent. The blood urea nitrogen was 35 mg. per cent, creatinine was 2.2 mg. per cent, carbon dioxide-combining power was 14.3 mEq. per L., and the prothrombin time was 64 per cent of normal. A single SGOT determination 8 hours after onset of pain was 135 units. An electrocardiogram taken several hours after admission showed normal sinus rhythm with a rate of 150, the pattern of left ventricular hypertrophy, and depressed S-T segments in leads I, II, aV_L, and in the lateral precordial leads. The electrocardiographic changes were interpreted as indicating left ventricular hypertrophy and "strain," with S-T depression suggestive of acute coronary insufficiency.

On admission the patient was placed in an oxygen tent and was given meperidine (Demerol) for pain. Despite relatively large amounts of norepinephrine by intravenous infusion the blood pressure remained at a relatively low level, and she steadily weakened, and died 32 hours after admission.

Autopsy disclosed a moderately distended ascending aorta with an extremely soft wall. A 3.0-cm., irregular, longitudinal tear was present on the external surface 2.0 cm. above the aortic ring. A 2.0-cm. horizontal tear was noted on the intimal surface 5 cm. above the aortic ring with dissection of the wall from the arch to the aortic ring. The proximal ends of the innominate left common carotid, and left subclavian arteries were involved in the dissection. Inferiorly, the dissection extended through the aortic ring into the pericardium, which was filled with blood and blood clots. The interatrial septum was moderately distended and on section was found to be dissected and filled with blood clots. The dissection of the interatrial septum extended for a distance of 3.0 cm. and microscopically the dissection appeared to be fresh. The erythrocytes within the muscle were intact and there was no evidence of myocardial necrosis in tissue stained by hematoxylin and eosin and no leukocytic infiltration had occurred.

Aside from moderate thickening (2.0 cm.) of the left ventricular wall, examination of the heart was otherwise not remarkable. The coronary arteries were patent throughout, and their walls were free from dissection. Microscopic examination of numerous sections of the left ventricle showed no evidence of myocardial infarction. Each pleural cavity contained about 200 ml. of hemorrhagic fluid and areas of hemorrhage were noted in both hilar regions. Microscopic examination of the liver showed acute passive congestion with actual necrosis at the lobular centers, which was interpreted as occurring within a few hours before death. No other significant abnormalities were noted on gross or microscopic examination.

Case 3. A 53-year-old white woman was admitted to the hospital on June 9, 1957, because of severe upper and middorsal pain, radiating to the costal margins anteriorly and into the left arm. The pain began suddenly 4 hours prior to admission and was accompanied by sweating and vomiting. There was a history of a vague type of anterior chest pain over the preceding 2 years, which was precipitated by exertion and relieved by rest. No history of hypertension or of diabetes mellitus was obtained, but a chest x-ray done 1 year previously showed dilatation of the arch of the aorta without calcification of the aortic wall.

Physical examination showed an agitated, acutely ill woman, complaining bitterly of pain in the interscapular area. Good pulsations were noted in both common carotid and femoral arteries, and the blood pressure was 140/90 in both arms. General physical examination was not remarkable save for evidence of slight enlargement of the heart to the left and a grade II apical systolic murmur.

During the patient's hospital course of 10 days she had intermittent bouts of severe middorsal pain, radiating to the costal margin anteriorly. Serial chest x-rays showed a rapid increase in size of the arch of the aorta, but peripheral arterial pulsations remained normal. The routine laboratory data were not remarkable. Serial electrocardiograms remained within normal limits. On June 19 the patient was transferred to the Georgetown University Hospital, where operation was performed on June 20 by Dr. Charles Hufnagel. A dissecting aneurysm of the thoracic aorta was found with its point of origin just distal to the origin of the left subclavian artery. Three inches of tortuous aorta, including the site of origin of the dissection, were resected, the clot was removed from the aortic wall inferiorly to the diaphragm, and the area of dissection was obliterated by sutures.

The SGOT activity was 21 units on June 9 and on June 10 and 8 units on June 19. Her postoperative course was very satisfactory except for paralysis of the recurrent laryngeal nerve and thrombophlebitis of the right leg, which was treated successfully with Dicumarol without peripheral hemorrhage or increase in size of the thoracic aorta.

Discussion

A summary of the SGOT determinations in the 3 cases is given in table 1.

Review of the medical literature indicates that abnormally high serum GOT activity has been noted in the following conditions: acute myocardial infarction;[2, 4-6, 10] myocarditis, rheumatic[6] and granulomatous (Fiedler's);[9] cardiac arrhythmias with ventricular rate of 160 and over;[6] acute hepatitis, hepatic cirrhosis, and obstructive jaundice;[6] pancreatitis (50 per cent of cases), with jaundice (75 per cent);[6] crush injuries involving muscle;[9] embolus to extremity;[6] surgical trauma;[7, 9] pulmonary embolism (usually late in the course of the disease and associated with icterus);[6, 9] hemolytic crisis;[9] dermatomyositis;[8, 13] experimental ligation of renal, mesenteric, splenic, and pulmonary arteries;[6] and disseminated lupus erythematosus.[13]

While no mention is made of SGOT determinations in the presence of pericardial tamponade, it is of interest in connection with cases 1 and 2 that pericarditis is generally associated with normal GOT activity in the serum.[2, 9, 10] However, in certain series, "false positives" have been reported, the incidence being from 0 to 75 per cent.[6] Experimental pericarditis, induced in dogs by insufflation of talc into the pericardial cavity, has been shown to produce elevation of serum GOT activity, only if associated with subepicardial myocardial necrosis.[12]

Table 1.—*SGOT Values following Onset of Dissecting Aneurysm of the Thoracic Aorta, in Units*

Case no.	Day after onset of dissection						Pericardial tamponade
	1	2	3	4	5	10	
1	115	—	82	40	17	—	Yes
2	135	—	—	—	—	—	Yes
3	21	21	—	—	—	8	No

Cases 1 and 2 showed no evidence of any of the above states known to be associated with elevated GOT activity, but the possibility is suggested that GOT may have been liberated in sufficient quantity from the hemolyzed dissecting blood to give rise to an elevated level in the serum. Since whole blood hemolysates have been shown to have a GOT activity 10 times that of serum,[11] it is apparent that 1 ml. of whole blood could release 300 units of GOT. Hemolysis of 1,000 ml. of blood would be required to produce the amount of GOT contained in 1 Gm. of heart muscle, and the infarction of this small amount of cardiac muscle could scarcely be expected to produce serum transaminase levels of the magnitude recorded in cases 1 and 2. In view of the relatively low concentration of GOT in the human erythrocyte, it is evident that if hemolysis were the only factor accounting for the observed rise in GOT titer in cases 1 and 2, gross hemolysis of the serum should have been noted, but none was present. Moreover, our case 3 and the one reported by Kattus et al.[2] had normal values, a finding that would not be expected were hemolysis the explanation of the elevated GOT.

Another explanation is that the elevation of GOT in cases 1 and 2 is the result of presence of blood in the pericardial sac, which

was not involved in case 3. While no significant morphologic changes were noted in cardiac muscle, case 2 showed dissection into the interatrial septum and it is entirely possible that some muscle damage, without evident morphologic change, may have resulted from the intrapericardial hemorrhage with release of GOT. It may be concluded that the mechanism of the elevation of GOT in these 2 cases is currently not well understood, but it is quite clear that SGOT determination is not always a reliable method in the separation of the clinical entities of myocardial infarction and dissecting aortic aneurysm.

Summary

Three cases of dissecting aneurysm of the thoracic aorta are presented, 2 showing distinct elevation in serum glutamic oxaloacetic transaminase (SGOT) levels. Elevation of SGOT level was associated with extension of the dissection into the pericardial sac. Possible explanations for the rise in SGOT level in dissecting aortic aneurysm are discussed.

Summario in Interlingua

Es presentate 3 casos de aneurysmo dissecante del aorta thoracic. Duo exhibiva un elevation distincte del nivellos de transaminase glutamic-oxaloacetic del sero (TGOS). Le elevation del nivellos de TGOS esseva associate con le extension del dissection a in le sacco pericardial. Explicationes possibile del augmento del nivellos de TGOS in dissecante aneurysmos aortic es discutite.

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Changing Frequency of Arteriosclerosis in Mammals and Birds at the Philadelphia Zoological Garden

Review of Autopsy Records

By H. L. Ratcliffe, Sc.D., and M. T. I. Cronin, M.R.C.V.S., Ph.D.

From 1901 through 1932 arteriosclerosis was found in less than 3 per cent of autopsies on mammals and birds at the Philadelphia Zoological Garden, but thereafter its frequency has increased to about 20 per cent. This study has attempted to identify factors that may be associated with this change in frequency.

A CONSIDERABLE volume of clinical and experimental evidence supports the opinion that the frequency of arteriosclerosis in human populations is determined to a large degree by the level of dietary fats.[1-7] However, other studies suggest instead that the development of this disease reflects the interaction of several factors some of which, at least, are not related to fat intake.[8-11] The observations to be reported here support the latter view, insofar as it may apply to captive wild mammals and birds.

Material

The material used in this review was collected over a period of 40 years, January 1, 1916, to January 1, 1956. During the greater part of this period the late Herbert Fox, M.D., supervised its collection. One of us (H. L. R.) assisted Dr. Fox from August 1929 until his death early in 1942, and succeeded Dr. Fox in the direction of this work. Thus the standards of observation, collecting, and recording have been reasonably uniform throughout the period of this study.

During the initial 20 years of this period, nutritional disease was a common cause of death among the animals of this Zoo and arteriosclerosis relatively uncommon.[12, 13] But in 1935 the traditional and often inadequate diets then common to zoological gardens were replaced by controlled diets.[14, 15] Under these conditions arteriosclerosis has developed much more frequently.

The diagnosis of arteriosclerosis in these animals has been based upon macroscopic and microscopic examination of the aorta, heart, and other organs of the body cavities. Vessels of the extremities rarely have been studied. Intimal thickening, whether accompanied by signs of lipid deposits or by changes in the media, has been taken as evidence of the disease. However, this does not include examples of intimal thickening that might be interpreted as having developed in association with inflammatory lesions in or adjacent to the wall of an artery.

Our practice has been to ignore small isolated plaques of the aorta and its larger branches unless these were accompanied by vascular disease of the heart, kidney, or spleen. But we have included animals in which lesions of the arteries of the heart and kidneys were not accompanied by disease of the aorta.

In routine practice tissues were embedded in paraffin and stained with hematoxylin and eosin. During the present study additional sections have been prepared from selected cases by the following methods: Gomori's reticulum stain, Verhoeff's elastic stain, and Lillie's allochrome stain.

Few of the animals in this series were born in captivity. Thus age at death rarely may be stated accurately, but must be given as the "exhibition age," i.e., the length of life in the Zoo. Inaccuracies from this source are distributed about equally to all taxonomic groups, for wild animals usually are imported as immature specimens.

Age may be expressed most conveniently in months, because a majority of deaths fall into the lower age groups, which reflects the high mortality of animals in zoos. In discussing age we shall have occasion to refer to estimates of "potential longevity." The basis for these estimates was outlined earlier, although present evidence demands some upward revision of the published values.[16]

During the period of this review arteriosclerosis was found in mammals of 45 families and in birds of 65 families. These groups are represented in the records by 3,360 and 7,660 autopsies, with 360

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TABLE 1.—*Diets*

Families	1916 to 1936	1936 to present
1. Cervidae 2. Bovidae	60-70% of intake equal parts (by volume) cracked corn, crushed oats, wheat bran; balance—timothy and clover hay, about 3% fat.	60-70% of intake the following mixture (parts by weight) Codliver oil 0.135 Ground oats 4.5 Iodized salt 0.45 Ground wheat 4.5 Oystershell flour 1.125 Brewers' grains 4.5 Brewers' yeast 2.34 Ground corn 6.75 Alfalfa leaf meal 11.7 Dry beet pulp 45.0 Linseed meal 4.5 Chopped carrots or kale 10.0 Balance—alfalfa, timothy, and clover hay for Cervidae and Bovidae; alfalfa hay, kale, and carrots for Macropodidae. About 3% fat.
3. Macropodidae	40-50% of intake bread*; balance—potatoes, carrots, beets, apples, lettuce. About 2% fat.	
4. Sciuridae	60-70% of intake bread*, corn, sunflower seed; balance—carrots, beets, etc. About 2% fat.	
5. Capromyidae 6. Dasyproctidae	40-50% of intake bread*; balance—potatoes, carrots, beets, etc. About 2% fat.	70-75% of intake the following mixture (parts by weight) Ground corn 10.5 Dry skim milk 7.0 Ground wheat 10.5 Oystershell flour 1.4 Ground barley 7.0 Iodized salt 0.7 Ground rolled oats 7.0 Alfalfa leaf meal 3.5 Peanut meal 7.0 Codliver oil 1.4 Soybean meal 7.0 Ground boiled meat 10.0 Brewers' yeast 7.0 Meat broth 20.0 Balance—kale and carrots (Pongidae—kale and oranges). About 5% fat.
7. Cebidae 8. Cercopithecidae 9. Pongidae	70-80% of intake bread*, boiled rice, bananas, potatoes; balance—apples, lettuce, onions; except Pongidae for which milk and eggs supplied about 5% of intake. About 2% fat.	
10. Ursidae	40-50% of intake bread;* 20–25% meat; 20–25% suet; 2–3% fish; 3–4% carrots and apples. 15–20% fat.	Mixture for Capromyidae, etc. 30–40% Mixture for Procyonidae, etc. 20–25% Suet 15–30% Fish 10–12% Carrots 5– 7% 15–20% fat.
11. Procyonidae	50–55% intake meat; 10–12% fish; 35–40% bread*; balance bananas, apples, carrots. About 8% fat.	Intake limited to the following mixture (parts by weight) Ground raw, unselected horse meat (10–20% fat) 86.0 Oystershell flour 4.8 Dry skim milk 3.6 Ledinac† 3.0 Codliver oil 2.0 Iodized salt 0.6 10–20% fat.
12. Mustelidae 13. Viverridae 14. Canidae	Intake limited to unselected ground or unground cuts of horse meat, with fat estimated to range from 10 to 20% by weight.	
15. Felidae		Unselected cuts of horse meat (10–20% fat by weight) with 2–3% mineral-vitamin mixture spread on the surface. Leopards—whole chickens (2-3 lbs.) twice weekly. 10–20% fat.

* A Zoo formula: molasses, bran, wheat and rye flour, yeast, and lard. About 5 per cent fat.
† A product of Lederle Laboratories, Pearl River, N. Y.

and 580 examples of the disease, respectively. However, about 65 per cent of the autopsies and examples of arteriosclerosis were from 15 families of mammals and 18 families of birds, which have been exhibited in approximately equal numbers during each half of the period of this study, i.e., 20 years before and 20 years after diets were improved.

Moreover, these 33 families have been represented in the records by about equal numbers of males and females, among which the disease has been about equally frequent. Thus, this review will be limited to the records of the 33 families and sexes will not be considered separately.

The 15 families of mammals and their diets before and after 1935 are listed in table 1.

Families 1 and 2 in table 1 are ruminants. The Cervidae are deer; the Bovidae include buffalo, goats, sheep, and antelopes. Family 3, Macropodidae, are the relatively large marsupials of Australia and adjacent islands—kangaroos, wallaroos, and wallabys—which are nonruminant herbivores.

Families 4, 5, and 6 are rodents. The Sciuridae include squirrels, prairie dogs, and woodchucks; the Capromyidae, coypus or nutria; the Dasyproctidae, agoutis and certain cavys.

Three families of primates follow. The Cebidae are New World monkeys: squirrel-, cebus-, spider-, and wooly-monkeys. The Cercopithecidae are the Asiatic monkeys, the African monkeys, and baboons. The Pongidae are anthropoid apes, represented here by gibbons, orang-utans, and chimpanzees.

Six families of carnivores complete the list. The Ursidae are bears, the most nearly omnivorous of the carnivores. The Procyonidae include raccoons, coatis, and kinkajous; the Mustelidae, mink, skunks, otters, and badgers; the Viverridae, civets, genets, paradoxures, and binturongs; the Canidae, wolves, foxes, and coyotes; the Felidae, tigers, lions, leopards, pumas, jaguars, and smaller cats.

Controlled diets were introduced during 1935 but the change was not completed for several months. Hence January 1, 1936, is taken as the start of the present feeding system.

Inspection of the chart shows that the earlier diets for herbivorous and omnivorous animals (families 1 to 10) were largely carbohydrate. Dietary protein was low even for herbivores, and certainly inadequate for rodents and primates. Vitamin and mineral supplements were not used. These defects were corrected by the current diets, which supply about 3 per cent of fat to herbivores and about 5 per cent of fat to omnivores (rodents and primates). These levels represent moderate increases over those provided by the earlier diets but still are well within the range of "low-fat" diets. Dietary fat for the carnivores was not changed materially.

As a rule the nutritional diseases that developed under the original system of feeding represented chronic deficiencies.[12, 14] Thus, in respect to caloric intake the animals were not undernourished.

We have not attempted to determine whether caloric intake has been changed by the improved rations, for among captive wild animals intake may be influenced by factors that are not related to the composition of the ration. Improved nutrition has been indicated by hair and feather growth, fecundity, and growth of young. Obesity rarely has been observed.

Observations

Mammals. During the period of this study 15 families of mammals whose records have been selected for review supplied 2,499 autopsies and 299 examples of arteriosclerosis. The distribution of these autopsies and examples of arteriosclerosis, by family, is given in table 2. Each family is listed in this table in the sequence used in the chart on diets (table 1). The autopsies for each family have been separated into those negative and those positive for arteriosclerosis, with the mean and median ages for each subdivision.

The number of autopsies for families of this series ranged from 37 (Dasyproctidae) to 423 (Cercopithecidae), and the frequency of arteriosclerosis from about 5 to 30 per cent.

With one exception, the Capromyidae, the mean and median ages of positive animals considerably exceeded the mean and median ages of the negative animals. These relatively low values for the negative animals usually reflect a high death rate, especially for the period before diets were improved. Thus, these records may be taken to suggest that arteriosclerosis generally has been associated with age, and occurred chiefly in that segment of each group that adapted to captivity and survived to advanced age.

Still, the differences between mean and median ages of the negative animals of many families, as well as the differences between the means of negatives and positives, show that their range in age often overlapped. Certainly, age has been a factor in the development of the disease, especially in its extent and severity, but age alone does not account for all differences in incidence.

A comparison of the average ages attained by animals of these 15 families is hampered by wide differences in their natural life spans. We have resolved this difficulty by the arrangement that is given in table 3. Here each family is listed in the sequence used in table 2, with its frequency of arteriosclerosis per 100 deaths, the mean ages of its negatives and positives expressed as fractions of potential longevity, its potential longevity, and the range in age of positive animals. This allows the frequency of arteriosclerosis in each fam-

TABLE 2.—*Arteriosclerosis in Mammals at the Philadelphia Zoological Garden**

Families	Negatives			Positives		
	Age at death: months			Age at death: months		
	Number	Mean	Median	Number	Mean	Median
1. Cervidae	280	50	40	23	85	85
2. Bovidae	260	50	50	38	145	135
3. Macropodidae	82	25	15	32	75	70
4. Sciuridae	202	15	10	12	70	65
5. Capromyidae	37	40	35	11	35	40
6. Dasyproctidae	25	40	65	12	104	95
7. Cebidae	197	20	15	17	50	25
8. Cercopithecidae	380	35	20	43	130	120
9. Pongidae	41	40	20	7	110	85
10. Ursidae	53	95	85	13	200	185
11. Procyonidae	133	35	30	19	70	75
12. Mustelidae	134	35	25	12	100	65
13. Viverridae	44	70	60	9	100	85
14. Canidae	180	35	30	30	80	75
15. Felidae	152	55	30	21	100	95
	2,200			299		

*Records for 15 families from January 1, 1916 through December 31, 1955; the number negative for arteriosclerosis for each family, with their mean and median ages in months, and the number positive with their mean and median ages also in months.

ily to be compared in terms of relative age at death (fraction of potential longevity). The values given here for potential longevity for each of these families are derived from the Lancaster formula.[16] They are believed to be accurate estimates in terms of this formula, as modified by more recent experience, and in a majority of families do not exceed ages attained by positive animals of the group.

The frequency of arteriosclerosis in this series of mammals has ranged from 5.6 per cent in the Sciuridae to 32.4 per cent in the Dasyproctidae. The Macropodidae has had the second highest frequency, 28.0 per cent; the Capromyidae third with 22.4 per cent; followed by the Ursidae and the Viverridae with 19.8 and 17.0 per cent respectively. Frequencies for the remaining carnivores, the primates, and the ruminants have overlapped.

The ratios of mean ages of negative and positive Sciuridae to potential longevity of this family suggest that the disease actually has developed chiefly in that segment of this group that chanced to survive for a reasonable fraction of its natural life span. Moreover, the higher frequencies for the Dasyproctidae and the Viverridae have been associated with proportionately higher values for both of these ratios.

On the other hand, these ratios for the Macropodidae, the Cebidae, and the Capromyidae, show arteriosclerosis developing in younger animals. Then too, these values for the Dasyproctidae and the Viverridae are approximately equal, while their frequencies of arteriosclerosis differ about 2-fold. In fact, the differences in frequency among the 15 families rarely seem to be correlated closely with the relative ages attained. Either we have erred in our estimates of potential longevity or frequencies have been influenced by factors other than age. There is evidence to support this latter explanation.

For example, the higher frequencies of arteriosclerosis, 32 and 17 per cent, in the Dasyproctidae and the Viverridae respectively, have been associated with relative in-

TABLE 3.—*Arteriosclerosis in Mammals of Fifteen Families: Frequency, Ratios of Mean Ages of Negative and Positive Mammals of Each Family to Potential Longevity of the Family, Potential Longevity, and Range in Age of Positive Mammals*

Families	Per cent frequency of arteriosclerosis	Mean ages/Potential longevity		Potential longevity (months)	Range in ages (months)
		negatives	positives		
1. Cervidae	7.6	0.25	0.40	200	9—229
2. Bovidae	12.7	0.20	0.60	240	6—281
3. Macropodidae	28.0	0.12	0.35	200	1—198
4. Sciuridae	5.6	0.12	0.55	120	7—130
5. Capromyidae	22.4	0.20	0.20	180	6— 77
6. Dasyproctidae	32.4	0.35	0.60	180	7—193
7. Cebidae	9.6	0.07	0.15	300	1—221
8. Cercopithecidae	10.1	0.10	0.35	360	4—337
9. Pongidae	14.5	0.07	0.25	480	10—379
10. Ursidae	19.8	0.25	0.55	360	29—387
11. Procyonidae	12.5	0.20	0.40	180	6—177
12. Mustelidae	8.2	0.20	0.55	180	34—242
13. Viverridae	17.0	0.40	0.55	180	31—216
14. Canidae	14.0	0.20	0.45	180	3—172
15. Felidae	12.0	0.30	0.55	180	2—263

activity as well as with age. The cages for these animals are about 3 feet square and, as a rule, they have been caged separately.

Dasyproctidae are relatively large terrestrial rodents whose activity must be limited to cage floors. Moreover, these floors sometimes have induced persistent ulcers of the footpads of the animals, which further suppress activity. Seven of the 12 examples of arteriosclerosis in this family were associated with peripheral ulceration. Their ages ranged from 7 to 108 months. Other positive animals of this group survived from 96 to 193 months. Only one negative of the group, dead at 47 months, developed a focus of peripheral ulceration.

Viverridae are small nocturnal carnivores that climb easily. Thus their activity has not been limited to cage floors, for they also climb about the wire panels of the walls, which provide about 4 times the space allowed to Dasyproctidae. Moreover, their activity has not been hampered by ulcers of the feet. However, they rarely have been active animals.

Then, more than half of the examples of arteriosclerosis in the Macropodidae and Capromyidae (frequencies of 28 and 22.4 per cent) developed while these animals were exhibited, as expanding populations, in exhibition areas of constant size. Here, improved nutrition apparently has contributed to the frequency of arteriosclerosis by ensuring high-level reproductive drives in groups that lacked space for dispersion.

Thus, in the first decade of controlled feeding (1936 to 1945) 20 Macropodidae were exhibited and 5 died, 4 of which were positive for arteriosclerosis at ages ranging from 86 to 168 months (mean 130 months). None of the 9 young born during this period died of failure in lactation.

But from 1946 through 1955 purchases and births increased the number of Macropodidae on exhibition to 70 animals, with 43 deaths, approximately half caused by injury. Eighteen of the 32 positives for this family were found within this period. Their exhibition ages ranged from 1 to 198 months (mean 80 months) and only 5 of them were more than 99 months of age. Also within this period 10 nursing young (about half of all born but not included in the total for the group) died through failures in lactation.

And, in the Capromyidae, 10 of the 11 positives of this group were found within a 5-year period (1951 to 1955). They, and 11 negatives (all captive-born) died of injuries

TABLE 4.—*Arteriosclerosis in Mammals of Fifteen Families: the Records of 40 Years, Grouped by Five-Year Periods to Show the Number Negative for the Disease (N—) and Their Adjusted Mean Age, the Number Positive (N+) and Their Adjusted Mean Age, and the Frequency of Arteriosclerosis per 100 Deaths*

Periods	Death rate (per cent)	(N−)	Adjusted mean age (mos.)	(N+)	Adjusted mean age (mos.)	Per cent frequency of arteriosclerosis
1916–20	20	354	17	13	39	3.5
1921–25	21	373	20	16	34	4.0
1926–30	22	396	19	6	37	1.5
1931–35	16	314	17	48	43	13.0
1936–40	11	178	25	46	59	20.5
1941–45	8	144	20	40	43	21.7
1946–50	12	173	17	38	52	18.0
1951–55	15	268	15	92	40	25.5

within this period, at an age range of 6 to 58 months.

These 21 animals were from a breeding group that had increased rapidly for about 3 years. Then, as it neared a peak of about 30 animals, reproduction ceased and fights became increasingly frequent.

At autopsy the thyroid glands and adrenal cortex of these animals were hypertrophied, and spermatogenesis and oogenesis were suppressed, changes that were most pronounced in animals that died in the latter half of the 4-year period, when arteriosclerosis was most frequent and extensive. The eleventh positive animal of this family died at 77 months. It was one of 27 that had been exhibited singly or in nonbreeding groups prior to 1950.

These observations on the Macropodidae and the Capromyidae suggest that social pressure (group relationships) may contribute more than age to the frequency of arteriosclerosis. The increasing frequency of injury as a cause of death, as numbers increased, is evidence of mounting social pressure in these groups. Failures in lactation, suppressed spermatogenesis and oogenesis, as well as hypertrophy of the adrenal cortex and thyroid glands also are recognized as effects of rapidly developing social pressure.[17-20]

Thus, as illustrated by the records for the Dasyproctidae and the Viverridae, the range in frequency of arteriosclerosis in the families of this series (table 3) may reflect the effects of inactivity and age. Or, as illustrated by the records for the Capromyidae and the Macropodidae, age and inactivity may be overshadowed by the number in each exhibition group and their reproductive activity.

This series of mammals, as a whole, has had a 10-fold increase in the frequency of arteriosclerosis during the 40 years of this review (actually within the last 25 years). The first increases were associated with increasing age. More recently, however, mean ages have decreased while the frequency of arteriosclerosis has risen. These changes in frequency and age are illustrated by the values given in table 4, in which records of the series have been grouped by 5-year periods, and ages have been calculated as adjusted means, the number of positives (N+), their age in months, also as adjusted means, and the frequency of arteriosclerosis per 100 deaths.

The adjusted mean ages given in table 4 were derived from actual mean ages for each family at each interval, by the following method: Mean ages of negatives ($N_{\bar{n}}$) or of positives ($N_{\dagger\bar{n}}$) × 100/potential longevity = Correction Factors ($CF_{\bar{n}}$) or ($CF_{\dagger\bar{n}}$), which are used in the following formula to give the adjusted means:
$(N_{\bar{1}} \times CF_{\bar{1}}) + (N_{\bar{2}} \times CF_{\bar{2}}) + \ldots . (N_{\bar{n}} \times CF_{\bar{n}})/N_{\bar{1}} + N_{\bar{2}} + \ldots . N_{\bar{n}}$, and similarly for the positive animals.

Two sources of error are recognized in the values thus derived: exhibition ages, which do not allow for age on arrival, and the estimates of potential longevity. Since we are uncertain that these errors are truly random, we have omitted elaborate statistical tests for possible differences.*

Table 4 shows that arteriosclerosis was found in some 3 per cent of the mammals that died during the initial 15 years of this study (1916 to 1930). The fourth 5-year period,

*We are indebted to Dr. Leonard Berwick, Department of Pathology, University of Pennsylvania, for advice on the treatment of these data.

However, found an abrupt increase in frequency to 13 per cent. A lesser increase in the fifth 5-year period (1936 to 1940) brought the frequency to 20.5 per cent, at which level it continued through 1950, then increased to 25.5 per cent during the final 5-year period. Autopsies since 1955 indicate that this trend is continuing.

From 1916 through 1930 the Zoo maintained a relatively large number of mammals on exhibition and lost about 20 per cent of them annually. The onset of unfavorable economic conditions in 1930, followed by restricted commerce of World War II, caused a decrease in this population that continued through 1946. Subsequently, numbers have been increased, but had not returned to earlier values within the period of this study.[15]

The first increase in the frequency of arteriosclerosis coincided with decreases in the number on exhibition, which apparently improved the chances of survival of older animals. The increased number of positive animals and their increased mean age support this suggestion.

The introduction of controlled diets (1936 to 1940) was followed by further rises in frequency, but until the last 5-year period (1951 to 1955) these reflected the death rate rather than increased numbers of positives. The mean ages for both negative and positive animals during the fifth and sixth 5-year periods (1936 to 1945) suggest that the length of life in the Zoo was an important factor in maintaining frequency of arteriosclerosis. The new diets apparently contributed to frequency chiefly by improving the chances for survival.

Subsequently, however, the mean ages of the negative and positive animals have decreased in spite of adequate diets until, with the terminal 5-year period (1951 to 1955), these values equaled those of the 1916 to 1920 period. Meanwhile the frequency of arteriosclerosis continued at the 1936 to 1940 level for a decade, then increased to 25.5 per cent.

The last rise in frequency occurred in association with increasing numbers of animals on exhibition, and an over-all rise in injury as a cause of death.[21] Thus, it seems reasonable to suggest that improved diets have led to an increased frequency of arteriosclerosis by either of 2 mechanisms: increased life spans of relatively inactive animals, or increased vigor and reproductive drives. The second seems to have been the more important during the last decade of this study, especially the terminal 5-year period.

Birds. The diets for birds in this Zoo prior to 1935 ranged from complex mixtures of prepared foods, grain, seed, insect larvae, and fruit, through combinations of grain and seed, to lean meat and fish. The instructions for preparing these mixtures were vague at best, and the actual composition is known to have varied with the keeper on duty and the supplies on hand. Therefore an attempt to reduce these practices to a reasonable statement of food intake would be futile.

Since 1935, diets for birds have corresponded closely to or have been identical with those for mammals (see section on Mammals). These diets will be identified when particular groups of birds are discussed.

The 18 families of birds that have been selected for this review are represented in the records by 5900 autopsies and 456 examples of arteriosclerosis, a frequency of 7.7 per cent. From 1916 to 1931 arteriosclerosis was found in less than one per cent of these birds: 20 of 3181 autopsies.

The changes in frequency and age by 5-year intervals during the period of this study are shown in table 5. The values for the adjusted mean ages given in this table were derived by treating the records for these birds by the methods described for table 4. In applying this method to the birds we have used the maximum exhibition age for each family to the closest multiple of 10, instead of potential longevity, as the factor from which adjusted mean ages might be computed. This seemed the better course, since we are uncertain that we have sufficient data for applying the Lancaster formula for potential longevity to birds.

The frequency of arteriosclerosis by 5-year

TABLE 5.—*Arteriosclerosis in Birds at the Philadelphia Zoological Garden: Records of Eighteen Families for Forty Years, Grouped by Five-Year Periods to Show the Number Negative for the Disease (N—) and Their Adjusted Mean Age, the Number Positive (N+) and Their Adjusted Mean Age, and the Frequency of Arteriosclerosis per 100 Deaths*

Periods	Death rate (per cent)	Negatives		Positives		
		(N−)	Adjusted mean age (mos.)	(N+)	Adjusted mean age (mos.)	Per cent frequency of arteriosclerosis
1916–20	23	1160	8	5	35	0.4
1921–25	23	1185	9	6	36	0.5
1926–30	21	811	14	9	30	1.0
1931–35	18	548	14	89	34	14.0
1936–40	13	452	18	38	46	7.7
1941–45	10	305	20	96	34	24.0
1946–50	15	576	11	100	40	14.7
1951–55	13	497	10	113	30	21.7

periods in this series of birds has fluctuated more than in the mammals. Still, as in the mammals (table 4), the first pronounced increase in frequency came within the fourth 5-year period (1931 to 1935), prior to the change in diets and in association with decreases in the number on exhibition and annual death rates, and increases in mean age at death for both negatives and positives.

Then, in the 5-year period immediately after the new diets were introduced the number of positives (and the frequency) dropped to about half that for the preceding 5-year period, even though mean ages of both negatives and positives were increased. Subsequently the number of positives has increased with each succeeding period while mean ages dropped until they again equalled those for 1916 to 1920.

Changes in the number of birds on exhibition in this Zoo have paralleled closely those in the mammals. The decrease ended in 1946, and within the following decade (especially since 1950) purchases and breeding have returned the number on exhibition to that of the period from 1916 through 1925.

Thus, as in the mammals, age apparently contributed to the first increases in arteriosclerosis. However, the further increase in age that came with improved nutrition seemed to reverse this trend, while the more recent rises in frequency have been accompanied by decreasing age. Autopsies since 1955 indicate that the latter trend is continuing. At the same time arteriosclerosis has come to be a relatively frequent cause of death rather than an incidental lesion.

Tables of the records for individual families of birds reveal nothing that is not already evident from tables 2 and 3 for mammals. However, the range in frequency has been greater among birds, from less than 2 to more than 30 per cent.

The groups in which less than 5 per cent have been involved are represented in this series by about 3500 autopsies. These groups include only the smaller omnivorous birds, finches, sparrows, starlings, troupials, doves, and parakeets, all of which have been exhibited in enclosures that have allowed them to maintain a high order of activity. Few of these birds have had opportunities for breeding, although seasonal nest-building activity has followed improvements in feeding.

The diets for these birds, after 1935, supply upwards of 12 per cent of fat which is at least a 2- to 4-fold increase over that supplied by earlier foods. Their relatively small increase in arteriosclerosis after 1935 may be explained, however, by increases in exhibition age.

The higher frequencies of arteriosclerosis have been found chiefly among larger birds that have little tendency to or opportunity for approximating natural activity. These groups include pheasants, ducks, geese, swans, the larger psittacine birds such as cockatoos, parrots, and macaws, and the storks, herons, hawks, and eagles, i.e., both omnivorous and carnivorous birds.

Among the cranes, storks, and herons especially, inactivity often has been augmented by chronic inflammatory lesions of the feet. However, the records do not permit an estimate of the importance of this combination of factors to the frequency of arteriosclerosis generally. The most convincing evidence provided by the birds for this asso

iation was the death of 4 shoebill storks *Balaeniceps rex*) of arteriosclerosis within 5 ionths after the peripheral lesions developed. 'heir exhibition ages ranged from 8 to 238 ionths.

Since 1935 the omnivorous birds have re-eived a diet that is identical with or that orresponds closely to the current diet for rimates. Hawks and eagles have been fed he ground meat ration that was designed or the Procyonidae and other carnivorous nammals, while storks and herons have re-eived only fish or fish in combination with his meat mixture. These mixed rations for primates and carnivores allow fat intake of bout 6 and 15 per cent for the omnivorous nd carnivorous birds, respectively, which re estimated to be about a 2-fold increase ver levels available before 1935.

Both dietary types of birds have had approximately the same changes in frequency of arteriosclerosis in association with changes in mean ages shown in table 5. Thus, apparently, diets and dietary fat have not been a factor in these changes. Moreover, the current diet for parrots, macaws, and cockatoos has reduced dietary fat from about 25 to about 6 per cent. During the period of 20 years following this change these birds had only a 2-fold increase in age while the frequency of arteriosclerosis increased about 6-fold.

As mentioned earlier, improved nutrition has increased reproductive drives. These have been much more evident among the larger types of birds than among the smaller ones. On the whole, however, successful breeding has been limited to ducks and their relatives, and to pheasants and cranes which, n spite of restricted space and increasing opulation, maintain a reasonable level of roductivity. Young usually have been parated from adults immediately after atching.

Still, irrespective of success in breeding or e presence of suitable mates, the reproduc-ve drives of an adequately nourished popu-tion apparently result in pressures that in-ease with its density. The frequency of injury as a cause of death among these birds during the last decade of the present study is believed to reflect these increasing pressures.

Discussion

The material for this review represents records of routine autopsies on highly heterogeneous animals that died during a period of 40 years. Therefore inferences based upon this material must be presented cautiously.

Nevertheless, the frequency of arteriosclerosis in both mammals and birds has increased 10- to 20-fold during the period of this study. The more striking increases occurred within the last decade, 10 years after diets were improved, and in association with decreases in mean age.

This change has involved a wide variety of both mammals and birds and shows that, in the development of this disease, factors other than age or diets may have a major influence, the effects of which have not been limited to any one group of animals. Thus, a tentative identification of these factors should suggest new avenues for experimental and clinical investigation.

The records of this series through 1935 represent relatively malnourished animals among which successful breeding was rare.[14] To a large degree therefore, they must have lacked the reproductive drives normal to the animals that have been exhibited in this Zoo since diets were improved. Thus the number of animals on exhibition before 1936 was not reflected in mounting social pressure.

But since 1936 the intensity of social pressure seems to have increased as an exponent of the increase in population. The increasing frequency of injury as a cause of death, especially in breeding groups, and the loss of young through failure in lactation support this suggestion. It also is supported by observations on the development of social pressure within freely growing experimental populations.[18, 19] Therefore, we suggest that social pressure has been a major factor in the recently increased frequency of arteriosclerosis in mammals and birds of the Philadelphia Zoological Garden. Inactivity is believed to

have been a second factor. This has been particularly evident in animals that were caged alone.

Hypertrophy of the zona fasciculata of the adrenal glands has been one measure of increasing social pressure in freely growing experimental populations.[18–20] In the present series this change has been associated with the development of arteriosclerosis only in animals of the Capromyidae.

Other animals of this series may be regarded as having undergone partial adrenalectomy through more or less atrophy of the zonae fasciculata and reticularis of the adrenal cortex, because of reduced activity during life in the Zoo.[22] In these animals the zona glomerulosa and the medulla of the adrenal glands have been found to persist intact or to undergo hypertrophy. Presumably the adrenal glands of birds undergo corresponding changes with inactivity. For the present, however, the complex cellular patterns of avian adrenal glands usually have discouraged our attempts to demonstrate such changes.

The adrenal response of the Capromyidae and of the more rapidly growing experimental populations to increasing social pressure seems to differ from that common to other animals of this series. This difference possibly reflects the rate at which the stimulus has been applied. And actually the difference may be more apparent than real, for hypertrophy of the zona fasciculata in response to rapidly increasing social pressure may change the secretory pattern of the adrenal glands.[18–20] Presumably this change may contribute quite as much to an imbalance of the total output of the adrenal glands as if the zonae fasciculata and reticularis had undergone partial atrophy, while the medulla and zona glomerulosa were intact or hypertrophied.[23]

These considerations lead us to suggest that the primary factors in the observed increase in the frequency of arteriosclerosis in this series of mammals and birds has been an imbalance of adrenal secretion. Imbalance may follow inactivity, when animals are caged alone, or it may result from the development of social pressure in exhibition groups. This hypothesis is offered as a tentative explanation of the increased frequency of arteriosclerosis in mammals and birds in this Zoo. Its validity must depend, of course, upon appropriate experiments.

However, a preliminary test of the effects of inactivity on growing chickens has found that arteriosclerosis of the coronary arteries may develop within 11 weeks. Control birds that were allowed about a 10-fold greater space did not develop lesions within this period. Both groups were on a "low-fat" diet.[24]

Moreover, forced exercise (walking on a horizontal surface) is reported to protect chickens from the effects of feeding cholesterol in oil.[25] These results are in accord with observations on the frequency of coronary disease in human males in occupations that differ widely in their demands for muscular activity.[11] However, cholesterol-fed rabbits were not protected by forced exercise in a revolving drum.[26] In fact, the descriptions of the adrenal glands of these rabbits suggest that this form of exercise was quite as much of an abnormal stimulus as is rapidly developing social pressure.[18–20]

Summary

From 1916 to 1931 arteriosclerosis was found at autopsy in about 2 per cent of the mammals and birds that died in the Philadelphia Zoological Garden. But from 1931 to 1956 the frequency of this disease increased by about 10-fold in mammals and by about 20-fold in birds. This change in frequency began with decreasing populations and increasing age. It continued for a time after improved nutrition had given further increases in age. However, it has been most pronounced since 1946, when population densities were again increased, and mean ages decreased to about the levels of the 1916 to 1931 period. That is, the more recent increases in the frequency of the disease apparently have been independent of age and diets, but were associated with rises in popu-

lation densities. These observations suggest that social pressure, through an imbalance in adrenal secretion, has become a major factor in the frequency of arteriosclerosis in these animals.

Summario in Interlingua

Inter 1916 e 1931, arteriosclerosis esseva constatate in circa 2 pro cento del necropsias de mammales e aves que habeva morite al Jardin Zoologic De Philadelphia. Sed ab 1931 usque a 1956 le frequentia del morbo se decuplava in mammales e se vintuplava in aves. Iste disveloppamento comenciava con le reduction del populationes e con le augmento del etates. Le disveloppamento continuava durante un certe periodo de tempore post que un meliorate nutrition habeva resultate in augmentos additional del etates. Tamen, illo deveniva le plus marcate post 1946 quando le densitate del populationes reascendeva e le etates medie re-descendeva a circa le nivellos del periodo ab 1916 a 1931. Assi, le recente augmento in le frequentia del morbo esseva apparentemente indepeñdente de etate e dieta sed esseva associate con augmentos del densitate del population. Iste observationes suggere que le pression social—per imbalancia del secretion adrenal—ha devenite un factor de alte signification in determinar le frequentia de arteriosclerosis in iste animales.

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Medical Eponyms

By Robert W. Buck, M.D.

Moebius' Sign. The first mention of this sign was made by Moebius in a review of Pierre Marie's *Contribution à l'étude et au diagnostic des formes frustes de la maladie de Basedow*, Paris, 1883. The review appeared in Schmidt's *Jahrbücher der Inneren und Ausländischen Gesammten Medicin* 200: 100, 1883.

"Von Graefe has said that lessening or abolition of the synergic movement of the upper lids in raising and lowering the eyes is pathognostic. The reviewer has failed to find Graefe's symptom in a series of cases including some with and some without exophthalmos. He not only disbelieves in its pathognostic character, but considers it rather rare. On the other hand, the reviewer has recently observed a disturbance of convergence in two patients with Basedow's disease, both of whom had a moderate bilateral exophthalmos of equal degree. If the patient was asked to fix his vision upon the examiner's finger, both eyes looked to the right or to the left. That is, the patient fixed with one eye, and the external muscles of the other eye contracted consensually. On monocular examination, both internal recti functioned normally. In a third patient with exophthalmos, the symptom was absent. Whether the phenomenon is directly dependent upon the exophthalmus is uncertain."

The subject was again discussed, and observations in eight additional cases were reported in an article on "Convergence Insufficiency in Basedow's Disease" (*Ueber Insufficienz der Convergenz bei Morbus Basedowii*) which was published in the *Centralblatt für Nervenheilkunde, Psychiatrie und gerichtliche Psychopathologie* 9: 356-358 (June 15) 1886.

Pulmonary Valve Obstruction During Cardiac Catheterization

By Milton H. Paul, M.D., and Abraham M. Rudolph, M.D.

The clinical and hemodynamic responses to acute pulmonary valve obstruction during cardiac catheterization in patients with severe pulmonary valve stenosis are presented to illustrate the serious nature of this complication.

OBSTRUCTION of a stenotic pulmonary valve by the exploring cardiac catheter, a serious and not infrequent complication of cardiac catheterization, has received little attention in the literature.[1-4] Experiences in this laboratory indicate that pulmonary valve obstruction can occur both in a manifest, symptomatic form and in a concealed, asymptomatic form in patients with severe pulmonary stenosis. As catheterization studies are extended more generally to the infant age group and performed more often without anesthesia, the high incidence reported in this study may be more generally observed.

The purpose of this communication is to present clinical and physiologic observations during pulmonary valve obstruction and to derive from these a concept of the precarious hemodynamic status that exists in severe congenital pulmonary valvular stenosis.

Material and Methods

The data presented are derived from an analysis of 334 consecutive catheterization studies performed during an 18-month period in the Cardiopulmonary Laboratory of the Children's Medical Center, Boston. Pulmonary valve stenosis with intact ventricular septum was considered to be present on the basis of clinical and catheterization findings in 31 of these 334 patients. The ages of the patients ranged from 8 months to 15 years.

Right heart catheterization was performed on patients of all ages under mild sedation. Parenteral premedication was administered approximately 1 hour before catheterization in a dosage of 1 ml. per 30 pounds of body weight (meperidine 25 mg., phenothiazine 6.25 mg., and chlorpromazine 6.25 mg. per ml.).

Multiple blood samples for oxygen analysis were obtained from the superior vena cava, right atrium, right ventricle, and pulmonary artery. Whenever possible blood samples were procured simultaneously from the right ventricle or pulmonary artery and the exposed brachial or femoral artery. A 5F (1.6 mm. diameter) or 6F (2.0 mm. diameter) Lehman catheter was used to obtain intracardiac blood samples and pressure measurements. The oxygen saturation and oxygen capacity were determined by the spectrophotometric method of Gordy and Drabkin.[5] Pressure measurements were obtained with an electromanometer (Sanborn) or strain-gage manometer (Statham P23D) and recorded on a direct-writing oscillograph (Sanborn). The oxygen consumption was determined from measurements of the oxygen content and volume of the expired gas. Systemic and pulmonary blood flows were calculated by means of the Fick principle, and the pulmonary valve area was estimated from the Gorlin formula.[6]

The calculated systemic and pulmonary blood flows and pulmonary valve areas are not necessarily accurate, since certain assumptions have been necessarily extended. The oxygen consumption, when not measured, has been estimated at 180 ml. per minute per M.^{2} for infants and children. Furthermore, it has been assumed that the oxygen consumption remains unchanged during the period that the catheter is in the pulmonary orifice. Finally, in the cyanotic patients the calculated pulmonary blood flow is a minimum value, it does not include any collateral bronchial blood flow, and, in fact, represents flow across the pulmonary valve.

Results

In the course of diagnostic cardiac catheterization studies on 31 patients with pulmonary stenosis and intact ventricular septum, 8 patients (25 per cent) presented definite evidence that the cardiac catheter was ob-

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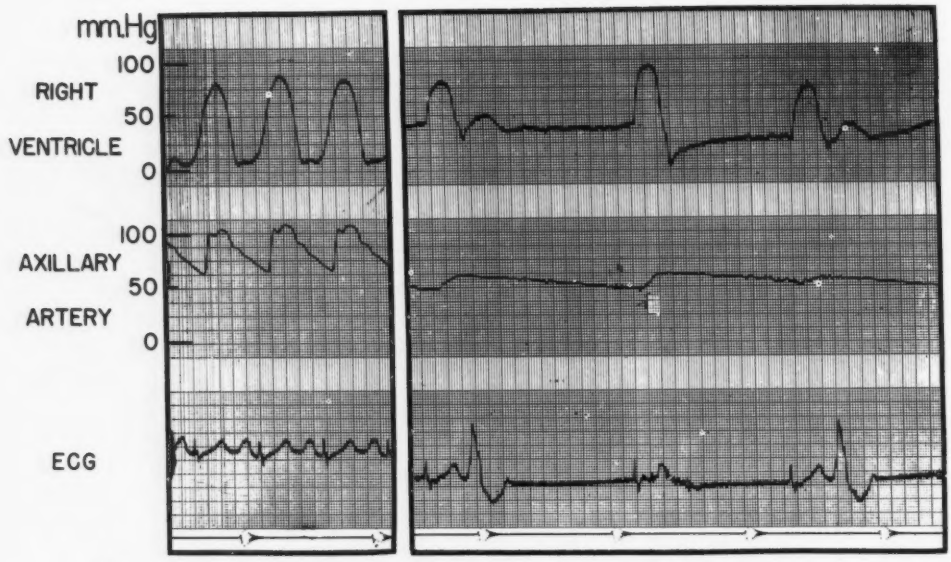

FIG. 1. Cardiovascular deterioration recorded 4 minutes after a 6F Lehman catheter was passed into the stenotic pulmonary valve of a 19-month-old infant.

structing blood flow through the pulmonary valve. Acute symptoms were experienced by 6 of these 8 patients when the cardiac catheter entered the stenotic pulmonary valve orifice.

Sudden restlessness was uniformly the earliest indication that the pulmonary orifice was obstructed and pulmonary blood flow reduced. Restlessness was rapidly followed by crying in infants and apprehension in older children. Increasing cyanosis was usually detected and bradycardia or tachycardia was often recorded. Finally, some neurologic reaction was frequently manifested, ranging from evanescent focal myotonic contractions in a single extremity to one instance of unilateral paresis of several days' duration. These reactions were observed between 4 and 13 minutes after the catheter had entered the pulmonary artery.

The acute, extreme cardiovascular deterioration that can occur is illustrated in figure 1. The first section of the tracing (*left*), obtained immediately before the catheter was advanced from the right ventricle into the pulmonary artery, shows normal cardiac rhythm, normal systemic blood pressure, and abnormally elevated right ventricular pressure. Approximately 4 minutes after the catheter had passed into the pulmonary artery the infant suddenly became restless and the previous mild cyanosis was observed to be intense. The catheter was immediately withdrawn to the right ventricle and the second section of the tracing (*right*) was recorded. The arrhythmia, bradycardia, and systemic hypotension persisted for several minutes and then the previous compensated hemodynamic status rapidly returned. This was the only instance of severe cardiac arrhythmia and cardiovascular deterioration that was observed.

Several hemodynamic changes were noted concurrent with pulmonary valve obstruction. The 31 patients with pulmonary valvular stenosis may be divided into 2 groups on the basis of the change in the oxygen saturation of the mixed *venous* blood before and after the cardiac catheter has entered the pulmonary orifice in each patient (fig. 2). It may be seen that no significant change in mixed *venous* blood oxygen saturation occurred in

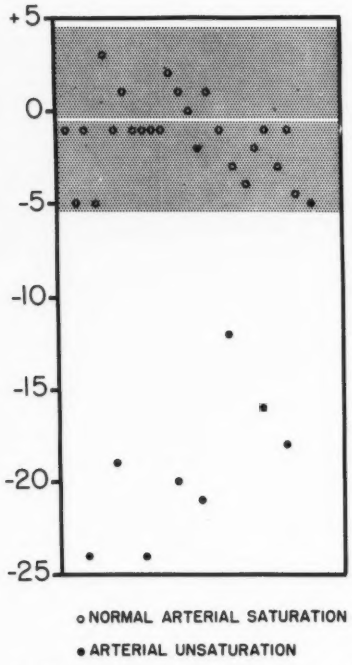

FIG. 2. Changes in per cent of mixed venous blood oxygen saturation (*ordinate*) based on the analysis of blood samples obtained before (right ventricle) and after (pulmonary artery) the cardiac catheter has been manipulated through the pulmonary valve. *Stippled area,* mean ± 2 S.D. change of per cent saturation in the 22 patients with normal resting arterial saturation.

those patients with normal *arterial* saturation at rest (*open circle*). In marked contrast, a striking decrease in mixed venous blood oxygen saturation occurred after the catheter was manipulated into the pulmonary artery in 8 of the 9 patients with resting arterial unsaturation (*solid circle*) due to an interatrial right-to-left shunt.

Similar observations were made on the systemic arterial oxygen saturation. The 22 patients with normal resting arterial saturation showed no change, but the 9 patients with arterial unsaturation had significant decreases in arterial oxygen saturation in response to acute obstruction of the stenotic pulmonary orifice. The most marked response resulted in a fall of the mixed venous oxygen saturation (pulmonary artery) from 39 to 8 per cent and a simultaneous fall in systemic arterial saturation from 51 to 18 per cent.

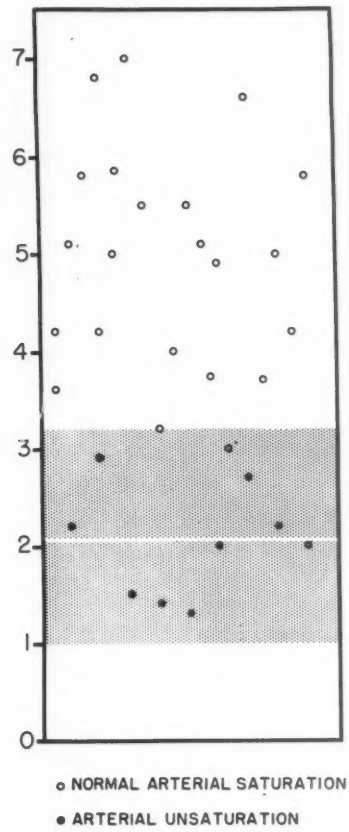

FIG. 3. Pulmonary valve blood flow (resting) L. per minute per M.^{2} (*ordinate*) in 31 patients with severe pulmonary valve stenosis. *Stippled area,* mean ± 2 S.D. pulmonary valve blood flow in the 9 patients with arterial unsaturation.

The pulmonary valve blood flow in the 31 patients with pulmonary stenosis was calculated on the basis of mixed venous blood samples obtained from the right ventricular outflow tract before the catheter entered the pulmonary artery (fig. 3). As expected, the patients with normal resting arterial saturation (*open circles*) had a higher pulmonary valve blood flow (mean 4.8 L. per minute per M.^{2}) than the group with resting arterial unsaturation (mean 2.1 L. per minute per M.^{2}).

No evidence of valve obstruction and no

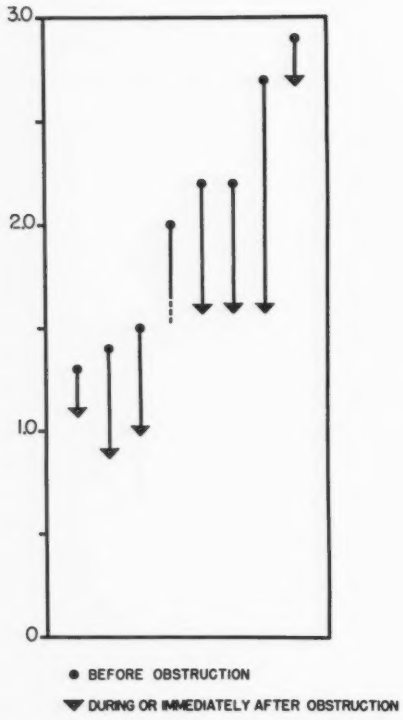

FIG. 4. Calculations of pulmonary valve blood flow L. per minute per M.^{2} (*ordinate*) in 8 patients with clinical and hemodynamic reactions indicating that the exploring cardiac catheter had significantly obstructed the pulmonary valve area.

change in pulmonary valve blood flow were observed in any of the 22 patients with pulmonary stenosis and normal arterial saturation. In contrast, clinical or hemodynamic signs of pulmonary valve obstruction were observed in 8 of the 9 patients with resting arterial unsaturation, and once the catheter entered the pulmonary orifice the pulmonary valve blood flow was further decreased from values already considerably below normal (fig. 4).

In order to assess the quantitative significance of these observations the calculated pulmonary valve areas of the patients with catheter obstruction have been compared with the valve areas of the nonobstructed group and with normal pulmonary valve area measurements. The normal pulmonary valve area

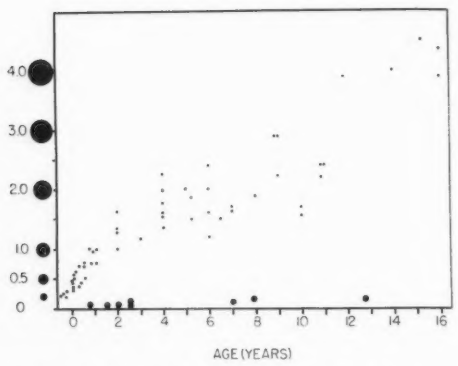

FIG. 5. Pulmonary valve areas in cm.^{2} (*ordinate*) calculated from measurements of heart valve circumference at autopsy. Small solid circles represent autopsy measurements of normal valve areas and larger solid circles represent 8 patients described in text with arterial unsaturation and valve obstruction reactions.

was calculated from measurements of the heart valve circumference in infants and children succumbing to an acute noncardiac death. It may be seen from figure 5 that the pulmonary valve area increases from about 0.5 cm.^{2} at birth to about 4.0 cm.^{2} at age 16 years. The 8 patients with pulmonary stenosis who manifested obstruction of the pulmonary valve uniformly had valve areas less than 0.15 cm.^{2} These valve areas are smaller than the average newborn pulmonary valve area and even less than the premature infant valve area. The patients with pulmonary valvular stenosis, normal resting arterial saturation and no obstruction with the cardiac catheter, all had pulmonary valve areas of 0.2 cm.^{2} or greater (fig. 6).

DISCUSSION

In our experience pulmonary valve obstruction during diagnostic catheterization has been a serious and not infrequent complication. The following sequence of events probably occurs in a patient with severe pulmonary stenosis and an interatrial communication when the cardiac catheter, passing into the pulmonary valve, further significantly reduces the orifice area. The right ventricle, already functioning under a

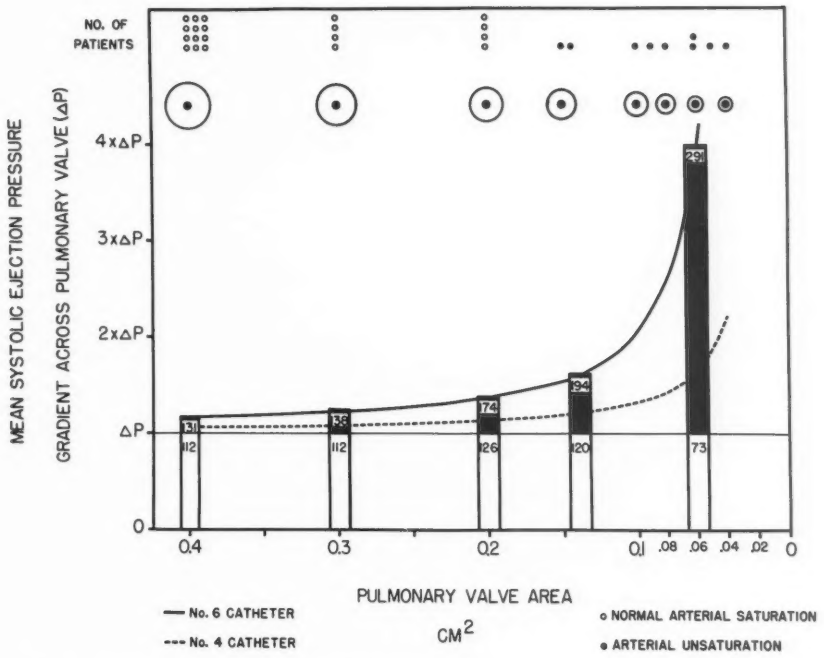

FIG. 6. Synthesis of the cardiac catheterization data and a theoretical analysis of the demands placed on the right ventricle by the introduction of a cardiac catheter into the severely stenosed pulmonary valve. Note the rapidly increasing and improbable mean systolic ejection pressure gradient (ΔP) that the right ventricle must generate in patients with valve areas less than 0.15 cm.^{2} if the stroke volume is to be maintained at the pre-obstruction level.

extreme load in the presence of severe pulmonary stenosis, is unable to increase significantly the mean systolic ejection pressure and thus fails to maintain the pre-obstruction pulmonary valve blood flow. The right-to-left shunt already present at the atrial level now increases and results in a marked fall in arterial oxygen saturation, increased cyanosis, and perhaps a central nervous system response to the anoxia. In this manner, the central nervous system reactions observed may be similar to the familiar cyanotic spells observed in patients with tetralogy of Fallot.

The analysis presented has been restricted to pulmonary stenosis with intact ventricular septum. A similar reaction in pulmonary valve obstruction might be anticipated in other congenital heart lesions if a critical pulmonary valve or infundibular stenosis and a proximal right-to-left shunt were present. Indeed, an episode of obstruction was observed in our laboratory in a 5-year-old patient with tetralogy of Fallot.

The inability of the right ventricle further to meet the demands caused by the catheter obstruction of the pulmonary valve can be analyzed in terms of the pressure gradients required to maintain an adequate blood flow through various valve areas. The vertical axis in figure 6 represents the mean systolic ejection pressure gradient, ΔP (expressed in mm. Hg), necessary to force a given stroke volume of blood through a given stenotic valve orifice.

Application of the Gorlin hydraulic formula[6] indicates that an increase in right ventricular pressure must occur in order to maintain the same stroke volume after the pulmonary orifice has been narrowed by the exploring cardiac catheter. The calculated

pulmonary valve areas of our patients with pulmonary stenosis are represented on the horizontal axis and range from 0.4 to 0.04 cm.^{2} If a 6F catheter (area of catheter tip is 0.03 cm.^{2}) is manipulated into a severely stenosed pulmonary valve of 0.10 cm.^{2} area or less, the right ventricle must provide a markedly increased pressure gradient ($3 \times \Delta P$ and $4 \times \Delta P$) to maintain the stroke volume at the pre-obstruction level. Thus, if a patient with a calculated pulmonary valve area of 0.4 cm.^{2} were to maintain the same right ventricular stroke volume before and after a 6F catheter was introduced into the valve, the mean systolic ejection pressure gradient across the pulmonary valve would increase from the observed 112 mm. Hg to the calculated 131 mm. Hg, a not improbable increase. If the same catheter were introduced into a stenotic pulmonary orifice of 0.06 cm.^{2}, the mean systolic ejection pressure gradient would have to increase from the observed 73 mm. Hg to 291 mm. Hg, a highly improbable increase.

The relative significance of the obstructing area of the exploring catheter in different valve areas can be easily visualized. In figure 6 the large open circles represent the pulmonary valve areas drawn to scale and the central solid circles represent the area occupied by a 6F cardiac catheter. It appears significant that a correlation is evident between the theoretical, calculated mean systolic ejection pressure curves and the clinical and catheterization data of the 31 patients under analysis. The 8 patients who had pulmonary valve obstruction during cardiac catheterization are cyanotic at rest and have pulmonary valve areas (0.15 cm.^{2} or smaller), which correspond to the steeply rising portions of the pressure curve (fig. 6). In contrast, the patients with normal arterial saturation have valve areas (0.20 cm.^{2} or larger), which correspond to the more horizontal portion of the pressure curve, and this group manifested no evidence of pulmonary valve obstruction.

If the complications of pulmonary valve obstruction during cardiac catheterization are to be prevented, continuous clinical alertness and electrocardiographic observations are essential. Accurate oximetric[3] monitoring of arterial saturation can provide an early warning of impending difficulties if anesthesia is utilized. Sudden restlessness, increasing cyanosis, or a significant change in the cardiac rate should lead without delay to withdrawal of the cardiac catheter from the stenotic pulmonary orifice.

Summary

In the course of catheterization studies performed on 31 patients with pulmonary stenosis and intact ventricular septum, 6 (20 per cent) experienced acute symptoms and hemodynamic changes after the cardiac catheter had entered the stenotic pulmonary orifice. Two additional patients had only hemodynamic evidence that the cardiac catheter was obstructing blood flow through the pulmonary valve.

Pulmonary valve obstruction in our experience has occurred only when severe pulmonary stenosis has been associated with a right-to-left shunt. The 8 patients presented with clinical symptoms or hemodynamic findings of acute pulmonary valve obstruction all had arterial unsaturation at rest and calculated pulmonary valve areas of 0.15 cm.^{2} or less.

Sudden restlessness, increased cyanosis, and tachycardia occurring after the exploring cardiac catheter has entered a stenotic pulmonary orifice are early signs that the pulmonary blood flow has been reduced.

Continuous clinical alertness, oximetric monitoring of arterial saturation, and electrocardiographic observation are essential, particularly in patients with resting arterial unsaturation, if the complications of pulmonary valve obstruction during cardiac catheterization are to be prevented.

Summario in Interlingua

In le curso de studios de catheterisation in 31 patientes con stenosis pulmonar e septo ventricular intacte, 6 (i.e. 20 pro cento) experientiava symptomas acute e alterationes hemodynamic post que le catheter cardiac

habeva entrate in le stenotic orificio pulmonar. Duo altere patientes manifesto solmente signos hemodynamic de que le catheter cardiac obstrueva le fluxo de sanguine a transverso le valvula pulmonar.

In nostre experientia, obstruction del valvula pulmonar ha occurrite solmente quando sever grados de stenosis pulmonar esseva associate con un derivation dextro-sinistre. Omne le 8 patientes qui se presentava con symptomas clinic o evidentia hemodynamic de acute obstruction del valvula pulmonar habeva non-saturation arterial in stato de reposo e calculate areas de valvula pulmonar amontante a 0,15 cm^2 o minus.

Un declaration subtite de disquietude, augmentos de cyanose, e tachycardia occurrente post que le catheter de exploration cardiac ha entrate in un stenotic orificio pulmonar es signos precoce de que le fluxo de sanguine pulmonar ha essite reducite.

Un continue vigilantia clinic, constante observationes del saturation arterial, e studios electrocardiographic es essential—specialmente in patientes con non-saturation arterial in stato de reposo—si le complicationes de obstruction del valvula pulmonar durante catheterisation cardiac vole esser prevenite.

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Hensler, L.: The Significance of the Venous Pulse in Constrictive Pericarditis. Cardiologia **30**: 114 (Feb.), 1957.

The author presents an analysis of phlebograms recorded in various types of constrictive pericarditis. On the basis of the relative size of a and c waves, and the degree and the timing of systolic and diastolic collapse (x and y) waves, 4 different patterns can be distinguished that are attributable to predominant involvement of the right or left chambers by the constriction. The 4 basic patterns were found in particular in localized forms of pericardial constriction, while the more extensive processes cause combination patterns or curves modified by alterations attributable to venous congestion. Regression and recurrence of pericardial constriction is exemplified by serial phlebograms recorded in a patient with tuberculous pericarditis who temporarily was treated by cortisone.

Pick

Steady-State Cardiac Output Determination During Combined Right and Left Heart Catheterization

By Philip Samet, M.D., William H. Bernstein, M.D., Robert S. Litwak, M.D., H. Turken, M.D., and Leonard Silverman, M.D.

Interpretation of the meaning of a mean diastolic atrioventricular gradient or a mean systolic ventricular-great vessel gradient requires simultaneous determination of the level of the gradient, the heart rate, and the cardiac output. The feasibility of steady-state Fick principle cardiac output determination during combined right and left heart catheterization is investigated.

LEFT heart catheterization[1-8] is a natural outgrowth of the development of mitral and aortic valve surgery and the resultant necessity for accurate preoperative evaluation of left-sided cardiac hemodynamics. Such evaluation requires simultaneous determination of valve gradient (systolic gradient for the aortic valve; diastolic gradient for the mitral valve), flow across the valve (cardiac output in the absence of valvular insufficiency), and heart rate. The first and third variables are readily determined during left heart catheterization. The purpose of this paper is to investigate the feasibility of steady-state cardiac output determination by the Fick principle, at rest and during exercise, in the course of combined right and left heart catheterization.

Methods and Material

Twenty-four comparisons of cardiac output at rest were performed in 23 patients, 11 women and 8 men with mitral valve disease, and 4 men with aortic valve disease. Right heart catheterization was performed, supine, in the usual manner, in the basal postabsorptive state, via a cutdown in the antecubital area. Brachial artery cannulation and open-circuit determination of oxygen consumption permitted calculation of cardiac output, generally in duplicate or triplicate. Left heart catheterization was then carried out in the prone position by a modification of the posterior percutaneous puncture technic of Fisher.[5] Two no.-17, thin-walled, 7-inch needles were inserted into the left atrium; polyethylene catheters were passed through the needles, one into the left atrium, and the other into the left ventricle. The needles were then removed over the catheters, leaving the latter in situ. The patient was then rotated back into the supine position. After a suitable rest period to permit restoration of the steady state, repeat cardiac output determinations were performed at rest, singly or in duplicate.

Ten comparisons of cardiac output during exercise were performed in 9 patients, 3 women and 5 men with mitral valve disease, and 1 man with aortic stenosis. All 9 are included in the above group of 23 patients. Exercise cardiac outputs during right heart catheterization alone were generally obtained in duplicate or triplicate before the commencement of left heart catheterization. Exercise cardiac outputs during combined right and left heart catheterization were carried out in the supine position, singly or in duplicate. A specially constructed bicycle wheel was employed in all exercise studies.

Blood gas analyses were performed on the Van Slyke manometric apparatus. Respiratory gas analyses were done on the micro-Scholander gas analyzer.

Results

The over-all cardiac output data at rest and during exercise are listed in tables 1 and 2. Cardiac indices at rest during right and during combined heart catheterization are recorded in table 1. The average cardiac indices are 2.48 and 2.45 L. per minute per $M.^2$ B.S.A. in the course of right and com-

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TABLE 1.—*Cardiac Output and Related Variables at Rest*

Subject	Cardiac index (L./min./M.² B.S.A.)			O_2 consumption (ml./min./M.² B.S.A.)			A-V difference (vol. %)			Respiratory quotient		
	Right	Combined	% deviation	Right	Combined	% deviation	Right	Combined	% deviation	Right	Combined	% deviation
1	2.59	2.79	+ 7	136	131	− 4	5.3	4.7	−12	.73	.74	+ 1
2	2.37	2.16	− 8	106	123	+16	4.5	5.7	+23	.77	.79	+ 3
3	2.12	1.94	− 9	123	111	−11	5.8	5.7	− 2	.73	.72	− 1
4	2.20	2.16	− 2	100	112	+11	4.6	5.2	+12	.97	.82	−17
5	1.76	1.78	+ 1	123	115	− 7	7.0	6.5	− 7	.80	.85	+ 6
6	2.51	2.72	+ 8	125	137	+ 9	5.0	5.1	+ 2	.92	.83	−10
7a	2.33	2.56	+ 9	118	119	+ 1	5.1	4.6	−10	.74	.80	+ 8
7b	2.43	2.24	− 8	125	112	−11	5.2	5.0	− 4	.81	.89	+ 9
8	1.29	1.24	− 4	100	87	−14	7.8	7.0	−11	.78	.85	+ 9
9	3.78	3.84	+ 1	123	119	− 3	3.3	3.2	− 3	.82	.87	+ 6
10	2.21	2.47	+11	120	128	+ 6	5.4	5.2	− 4	.69	.72	+ 4
11	2.46	2.47	0	106	114	+ 7	4.3	4.6	+ 7	.73	.89	+20
12	3.28	3.47	+ 6	113	125	+10	3.5	3.6	+ 3	.77	.78	+ 1
13	3.01	2.99	− 1	122	123	+ 1	4.1	4.1	0	.84	.90	+ 7
14	2.32	2.37	+ 2	136	138	+ 1	5.9	5.8	− 1	.82	.81	− 1
15	2.04	1.99	− 3	142	154	+ 8	7.0	7.7	+10	.89	.81	− 9
16	2.87	2.28	−23	139	128	− 8	4.9	5.6	+13	.78	.76	− 3
17	1.99	1.95	− 2	107	104	− 3	5.4	5.4	0	.81	.83	+ 2
18	1.91	1.77	− 7	102	102	0	5.4	5.8	+ 7	.83	.85	+ 2
19	1.76	1.93	+ 9	120	122	+ 2	6.8	6.4	− 6	.73	.83	+13
20	3.69	2.91	−24	155	162	+ 4	4.2	5.6	+28	.88	.87	− 1
21	3.96	3.93	− 1	161	151	− 6	4.1	3.9	− 5	.82	.87	+ 6
22	1.78	1.77	0	120	119	− 1	6.8	6.7	− 1	.81	.84	+ 4
23	2.79	3.19	+13	126	145	+14	4.5	4.6	+ 2	.81	.74	− 9
Average	2.48	2.45	7	123	124	7	5.2	5.3	7	.80	.82	6

TABLE 2.—*Cardiac Output and Related Variables during Exercise*

Subject	Cardiac index (L./min./M.² B.S.A.)			O_2 consumption (ml./min./M.² B.S.A.)			A-V difference (vol. %)			Respiratory quotient		
	Right	Combined	% deviation	Right	Combined	% deviation	Right	Combined	% deviation	Right	Combined	% deviation
5	2.23	1.95	−13	240	224	− 7	10.8	11.5	+ 7	.88	.99	+12
6	3.84	3.70	− 4	323	359	+11	8.4	9.7	+14	.90	1.03	+14
7a	3.59	3.26	−10	217	196	−10	6.1	6.0	− 1	.76	.79	+ 4
7b	3.04	2.77	−10	260	227	−14	8.6	8.2	− 5	.84	.85	+ 1
9	4.95	4.47	−10	272	259	− 5	5.5	5.8	+ 5	.97	.96	− 1
10	3.46	3.33	− 4	342	320	− 7	9.9	9.6	− 3	.80	.82	+ 2
12	4.66	4.78	+ 3	268	268	0	5.8	5.6	− 2	.87	.90	+ 3
13	3.32	3.06	− 8	193	208	+ 8	5.8	6.8	+16	.91	.90	− 1
14	2.68	2.70	+ 1	217	227	+ 5	8.1	8.4	+ 4	.85	.84	− 1
20	4.12	4.18	+ 1	270	293	+ 8	6.6	7.0	+ 6	.93	.90	− 3
Average	3.59	3.42	6	260	258	8	8.1	8.4	6	.87	.90	4

TABLE 3.—*Cardiac Output Data at Rest and during Exercise in Case 13 (Body Surface Area 1.60 M.²) on February 2, 1957*

Output number*	Cardiac output (L./min./M.² B.S.A.)	Oxygen consumption (ml./min./M.² B.S.A.)	A-V difference (vol. %)	R
1	3.08	126	4.1	.84
2	3.02	121	4.0	.85
3	2.93	120	4.1	.84
4 (3 min.)	2.92	178	6.1	.87(exer.)
5 (6¾ min.)	3.39	203	6.0	.92(exer.)
6 (8¾ min.)	3.25	182	5.6	.89(exer.)
7	2.99	123	4.1	.90
8 (6½ min.)	3.06	208	6.8	.90(exer.)

* The first 6 outputs were obtained during right heart catheterization alone; the last 2 outputs were obtained during combined heart catheterization.

TABLE 4.—*Cardiac Output Data at Rest and during Exercise in Case 14 (Body Surface Area 1.73 M.²) on November 29, 1956*

Output number*	Cardiac index (L./min./M.² B.S.A.)	Oxygen consumption (ml./min./M.² B.S.A.)	A-V difference (vol. %)	R
1	2.33	138	5.9	.77
2	2.30	136	5.9	.84
3	2.32	135	5.8	.84
4 (2½ min.)	2.49	192	7.7	.85(exer
5 (6¾ min.)	2.68	217	8.1	.85(exer
6	2.37	138	5.8	.81
7 (7 min.)	2.70	227	8.4	.84(exer

* The first 5 outputs were obtained during right hea study; the last 2 during combined heart catheterizatio

bined heart catheterization respectively. The average deviation, disregarding the sign of the deviation, is 7 per cent. In 20 of the 24 studies, the deviation was less than 10 per cent. There is no statistical difference between the mean values of 2.48 and 2.45 L. per minute per M.² noted above, $0.7 > p > 0.6$.

The oxygen consumption data are catalogued in table 1. The average oxygen consumption is 123 and 124 ml. per minute per M.² B.S.A., during right and combined heart catheterization respectively. There is no significant difference between these values, $0.5 > p > 0.4$. The average per cent deviation is 7 per cent.

The mean arteriovenous oxygen difference is also 7 per cent, table 1. The average values are 5.2 and 5.3 volumes per cent in the course of right and left heart catheterization respectively. These values again do not differ significantly, $0.6 > p > 0.5$.

The respiratory quotients (table 1) are virtually identical during right and combined heart study. The difference is not statistically significant, $0.3 > p > 0.2$.

The exercise data are portrayed in table 2. The average exercise cardiac index is 3.59 L. per minute per M.² B.S.A. during right heart catheterization and 3.42 L. per minute per M.² B.S.A. during combined cardiac catheterization. This difference is of questionable significance, $.05 > p > .02$. The 95 per cent confidence limits for the mean difference (0.17 L. per minute per M.² B.S.A.) are + 0.033 to + 0.305 L. per minute per M.² B.S.A. The average deviation is 6 per cent.

The agreement between levels of oxygen consumption (table 2) is excellent. The difference in mean values is not significant, $0.8 > p > 0.7$.

The mean exercise arteriovenous oxygen differences are 8.1 and 8.4 volumes per cent in the course of right and combined heart catheterization respectively, table 2. These values do not differ significantly, $0.2 > p > 0.1$. The mean per cent difference in arteriovenous difference is 6 per cent.

Table 2 lists the respiratory quotients during right and during combined heart catheterization. The mean values are 0.87 and 0.90 respectively, and are not significantly different, $0.2 > p > 0.1$.

Examples of the individual cardiac output data employed in construction of tables 1 and 2 are shown in tables 3 and 4. In table 3 outputs 5 and 6 were utilized to calculate the exercise outputs during right heart catheterization. Output 4 was obtained for another study, as was the fourth output in table 4.*

DISCUSSION

It is now generally agreed that interpretation of a mean diastolic atrioventricular and

*Outputs 4 in tables 3 and 4 were not used in calculating data of right heart exercise output.

if a mean systolic ventricular-great vessel gradient requires concurrent or simultaneous determination of flow across the valve. Use of the Fick principle to determine such flow requires demonstration that a steady state[10] may be achieved during combined right and left heart catheterization. Large errors in calculated flow may result otherwise.[11] There are as yet no published studies demonstrating that a steady state had been achieved either by the transbronchial or transthoracic technics, either at rest or during exercise. Such a demonstration requires correspondence of output data obtained by right heart catheterization with that obtained during combined heart catheterization in the course of the same study. If the Stewart-Hamilton technic is employed to determine cardiac output during left heart catheterization alone, relative constancy of flow during repeated determinations is required.

The data given in tables 1 to 4 indicate that determinations of steady-state Fick-principle cardiac output are feasible in the supine position, in the course of combined right and left heart catheterization, using the posterior percutaneous transthoracic puncture technic for left heart catheterization.

Summary

In 23 patients with rheumatic heart disease, comparison of cardiac output data during right heart catheterization alone and during combined right and left heart catheterization was made 24 times at rest and 10 times in the course of exercise studies. The results demonstrate that a steady state may be achieved during combined right and left heart catheterization.

Summario in Interlingua

In 23 patientes con rheumatic morbo cardiac, comparationes del datos de rendimento cardiac, obtenite in catheterismo dextro-cardiac sol e in catheterismo dextro- e sinistro-cardiac combinate, esseva completate 24 vices in stato de reposo e 10 vices durante exercitio. Le resultatos demonstra que un stato stabile pote esser effectuate in catheterismo dextero- e sinistro-cardiac combinate.

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Pulsus Alternans in Aortic Stenosis

Hemodynamic Observations in 50 Patients Studied by Left Heart Catheterization

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Alternation in the strength of left ventricular contractions was noted relatively frequently in patients with acquired aortic stenosis, but not in patients with congenital aortic stenosis of similar severity. The product of left ventricular systolic pressure and heart rate, an index of the myocardial oxygen requirement, was significantly higher in those patients who exhibited persistent pulsus alternans.

ALTHOUGH it has been recognized for many years that pulsus alternans may occur in patients with aortic stenosis,[1] the fact that these 2 conditions are frequently associated has not been documented. The presence of a stenotic aortic valve reduces the central aortic pressure, the central aortic pulse pressure, and also the magnitude of any alternation present in the aortic pressure pulse. Thus, in patients with aortic stenosis, the clinical detection of pulsus alternans in the peripheral pulse is difficult.

Left heart catheterization has made possible the direct measurement of left ventricular pressures in man and, therefore, even minimal alternations in the left ventricular pressure pulse are readily detectable. Furthermore, the technic of left heart catheterization facilitates the quantification of alternation and permits direct measurement of the duration of the events in the cardiac cycle. The purpose of this communication is to characterize the relationship between pulsus alternans and aortic stenosis in 50 patients in whom the presence of aortic stenosis was confirmed by the demonstration of a significant pressure gradient between the left ventricle and aorta at the time of left heart catheterization.

MATERIAL

Acquired Aortic Stenosis. The 28 patients with acquired rheumatic aortic stenosis ranged in age from 30 to 55 years and the average age was 41 years. There were 19 males and 9 females. In patients aortic stenosis was considered to be the sole valvular lesion on the basis of both hemodynamic and clinical evaluation. In 11 patients aortic stenosis was considered to be predominant although minimal aortic regurgitation or a mitral lesion was demonstrated or suspected. In the remaining 13 patients, aortic stenosis was present but was not considered to be the most important lesion hemodynamically; the majority of this group presented aortic regurgitation as the principal abnormality. In the entire group with acquired stenosis, the left ventricular-aortic pressure gradients ranged from 20 to 161 mm. Hg and averaged 74 mm. Hg.

Congenital Aortic Stenosis. The 22 patients in this group ranged in age from 6 to 36 years, and the average age was 16 years. Fourteen were male and 8 were female. The clinical features in these patients have been described elsewhere in detail.[2, 3] Of these patients, 5 had aortic diastolic murmurs suggesting associated aortic regurgitation. In none, however, was this lesion considered hemodynamically significant. Three patients exhibited, in addition to aortic stenosis, relatively mild degrees of pulmonic stenosis. In the 22 patients with congenital stenosis the left ventricular-aortic pressure gradients ranged from 15 to 172 mm. Hg and averaged 83 mm. Hg.

METHODS

In 46 patients left heart catheterization was performed by the transbronchial route. This technic has been described previously in detail.[4, 5] In 4 patients with congenital aortic stenosis, left ventricular pressures were measured by percutaneous puncture of this chamber through the anterior chest wall.[6] Arterial pressure measurements were made either in the central aorta by means of retrograde arterial catheterization[7] or by percutaneous puncture of the femoral or brachial artery. Left ventricular pressure, arterial pressure, and

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ıd II of the electrocardiogram were recorded ıultaneously on a multichannel cathode-ray ıotographic oscillograph. Paper speeds of 25 ıd 75 mm. per second were employed. The left ntricular-aortic pressure gradient was measured the difference between the peak systolic left ntricular pressure and the peak systolic aortic ressure. It is realized that in those patients in hom the femoral arterial pressure was used, the radient was underestimated, since femoral artery stolic pressure may exceed that in the central orta.[7, 8] In 3 patients with pulsus alternans in hom simultaneous left ventricular and central ortic pressures were recorded, the duration of left entricular isometric contraction was measured rom the onset of the left ventricular pressure scent to the onset of the central aortic pressure scent. The duration of total left ventricular ystole was measured from the onset of the left ventricular pressure ascent to the incisura of the entral aortic pressure pulse.

Results

Acquired Aortic Stenosis. In 15 of the 28 patients with acquired aortic stenosis persistent pulsus alternans was present in the left ventricular pressure pulse tracing. Four of the 13 patients without persistent alternans displayed the abnormality in several pulses following the occurrence of ventricular premature contractions. The magnitude of left ventricular alternation, i.e., the pressure difference between the large and small pulses, ranged between 2 and 43 mm. Hg and averaged 15 mm. Hg. Careful scrutiny of the arterial pressure tracings revealed that when left ventricular alternation was present, pulsus alternans could consistently be detected in the arterial pressure tracing. However, the magnitude of the alternation was strikingly reduced in the arterial pressure pulse. In several patients the arterial pressure tracings exhibited alternation of diastolic pressure (fig. 1). Concordant alternation of the left ventricular end-diastolic pressure was noted in 2 of the patients, while no distinct alternation of left ventricular end-diastolic or left atrial "a" point pressure could be detected in any of the other 13 patients. Electrical alternans was not noted in any of the electrocardiographic records.

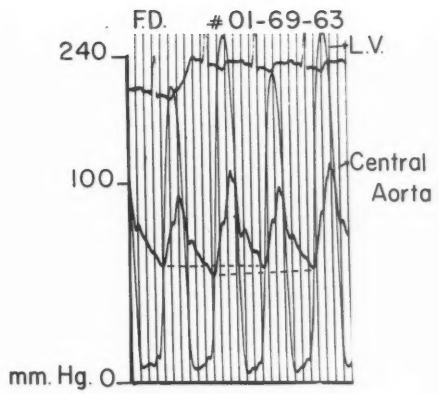

Fig. 1. Simultaneous left ventricular (LV) and aortic pressure pulses in a patient with severe aortic stenosis. Alternation of left ventricular, aortic systolic and diastolic pressures are apparent. Time intervals are 0.1 second.

In 3 patients with pulsus alternans in whom simultaneous left ventricular and central aortic pressure pulses were recorded, it was observed that left ventricular isometric contraction showed no evidence of alternation. In 1 of these patients, who had relatively severe left ventricular alternans (24 mm. Hg), there was concordant alternation in the duration of ventricular ejection and, therefore, also in the duration of total mechanical systole. In the other 2 patients, who had relatively mild left ventricular alternans (4 mm. Hg and 6 mm. Hg), there was no detectable alternation in the durations of ventricular ejection, or total systole. These findings are at variance with the observations of Katz and Feil[9] and of von Wallenstern.[10]

Right heart catheterization was performed in 24 of the 28 patients with acquired aortic stenosis. Right ventricular or pulmonary arterial alternans could not be detected in any of the patients who did not exhibit left ventricular alternans. However, 2 of the 13 patients with left ventricular alternans, in whom right heart catheterizations were performed, exhibited right ventricular alternans.[11] It should be noted that the right and left heart catheterizations were per-

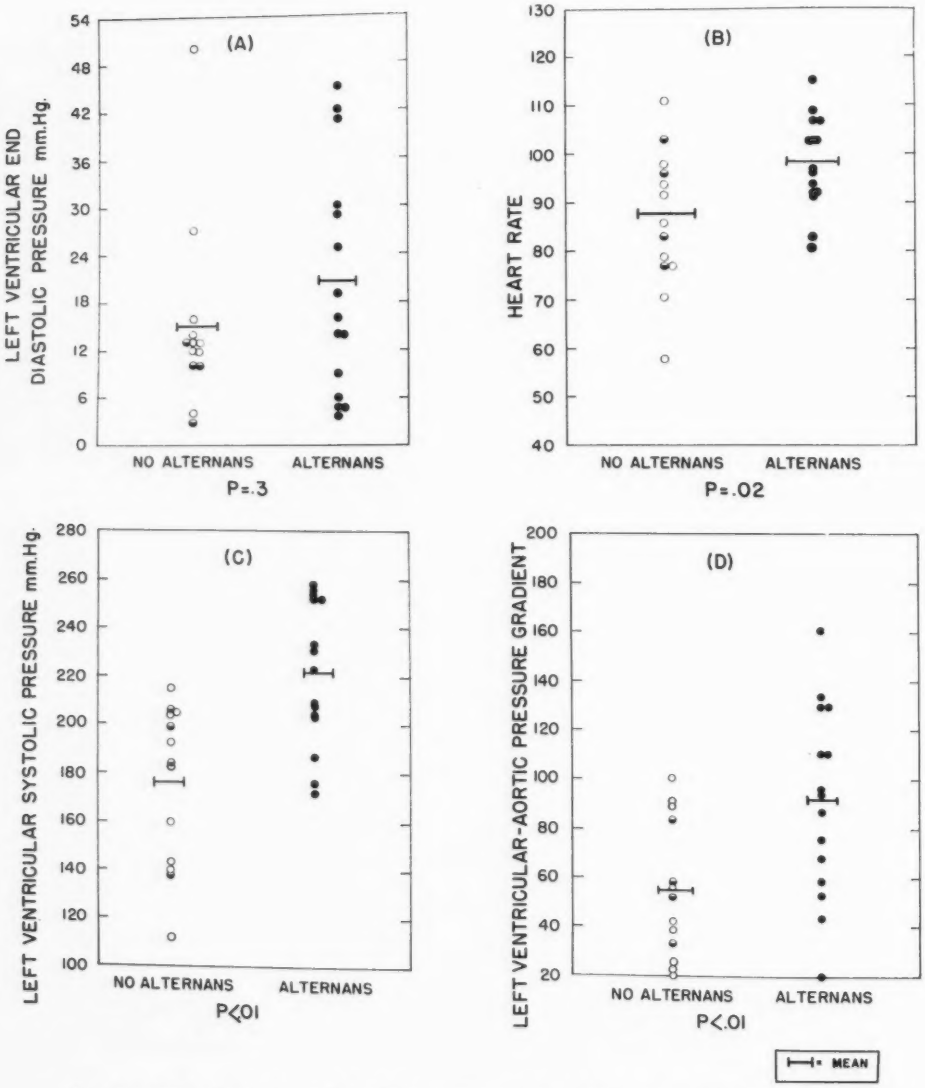

FIG. 2. Left ventricular end-diastolic pressures (*A*), heart rates (*B*), left ventricular systolic pressures (*C*), and left ventricular-aortic pressure gradients (*D*) in patients with, (closed circles), and without, (open circles), persistent pulsus alternans and acquired aortic stenosis. Half circles represent those patients who exhibited pulsus alternans for several beats following ventricular premature contractions.

formed several days apart and the conditions under which the measurements were obtained were not necessarily comparable.

There appeared to be little correlation between the age of the patient, the duration of symptoms, or the presence and severity of fatigue or syncope with the presence of persistent pulsus alternans. There was a distinct tendency for those patients who had exhibited severe congestive heart failure, angina pectoris, and marked cardiomegaly to have pulsus alternans; however, this was

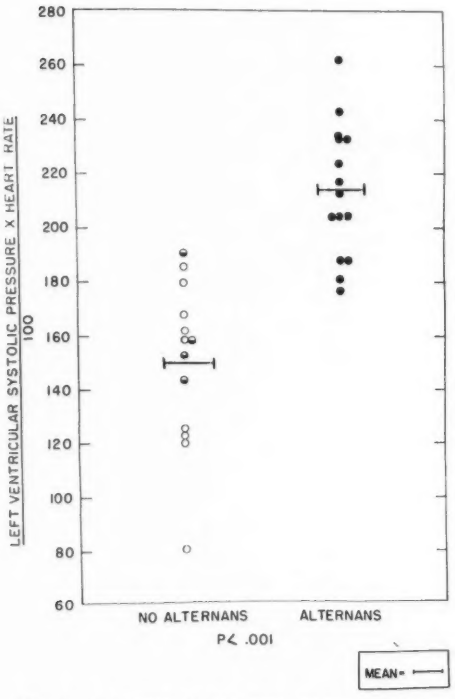

FIG. 3. Products of left ventricular systolic pressure and heart rate in patients with and without persistent pulsus alternans, and acquired aortic stenosis. Symbols same as in figure 2.

not a consistent relationship. Eleven of the 15 patients with persistent pulsus alternans had pure or predominant aortic stenosis. Of the 13 patients without alternans only 4 had pure or predominant aortic stenosis.

The presence of persistent pulsus alternans was related to a variety of hemodynamic parameters. No statistically significant separation was observed (fig. 2*A* and *B*) although the averages of the heart rates and of left ventricular end-diastolic pressures in the group with pulsus alternans were somewhat higher than in the group without alternans. The patients with pulsus alternans, however, had significantly higher left ventricular systolic pressures ($p < .01$) as well as significantly higher aortic valve gradients ($p < .01$) (fig. 2*C* and *D*). The hemodynamic parameter that afforded the best separation of the patients with pulsus

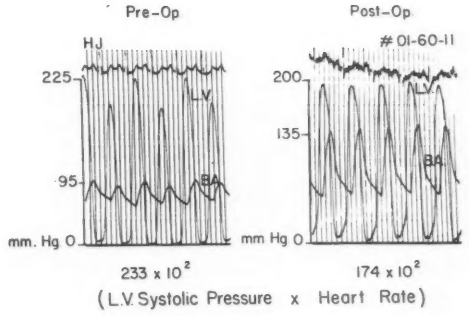

FIG. 4. Simultaneous left ventricular (LV) and brachial arterial (BA) pressure pulses and lead II of the electrocardiograms in a patient with acquired aortic stenosis before and after aortic valvulotomy. Note the absence of left ventricular and brachial arterial alternation following surgical relief of aortic stenosis, which effected a reduced left ventricular-aortic pressure gradient, a lower left ventricular systolic pressure, and a lower product of ventricular systolic pressure and heart rate. Time intervals are 0.1 second.

alternans from those without pulsus alternans was the product of the left ventricular systolic pressure and the heart rate (fig. 3). This relationship was statistically highly significant ($p < .001$).

Two patients with pulsus alternans were studied before and after aortic valvulotomy. In one patient it was observed that pulsus alternans was abolished following partial relief of the aortic obstruction and the concomitant lowering of the product of left ventricular systolic pressure and heart rate. This index fell from 233×10^2 to 174×10^2 (fig. 4). However, the other patient exhibited alternans both before and after operation. The product of left ventricular systolic pressure and heart rate showed little change (188×10^2 to 193×10^2).

Congenital Aortic Stenosis. Of the 22 patients with congenital aortic stenosis, none exhibited persistent pulsus alternans. Three patients, however, had transient periods of alternans following the occurrence of ventricular premature contractions. In the entire group of patients with congenital aortic stenosis the product of the systolic pressure and heart rate ranged from 83×10^2

to 361 $\times$ 10^2 and averaged 202 $\times$ 10^2. Two additional patients with congenital aortic stenosis exhibited persistent left ventricular alternans. They have not been included in this report because the left ventricular pressures were measured only at the time of surgical closure of an associated large patent ductus arteriosus.

Surgical Correlations. Of 11 patients with pulsus alternans who have been operated upon for acquired aortic stenosis 6 have survived operation and have shown various degrees of improvement. Five died during operation or in the immediate postoperative period. Of the 4 patients with acquired aortic stenosis without pulsus alternans who were operated upon, 3 survived operation and have shown various degrees of improvement and 1 died. Of the 12 patients with congenital aortic stenosis who were operated upon, all survived the operation.

Discussion

The fundamental mechanisms underlying pulsus alternans have not been completely elucidated.[11, 12] The present observations, when viewed in the light of previously reported data, suggest that a disparity between the oxygen requirement of the heart and the oxygen available to it may so alter myocardial contractility as to result in pulsus alternans. In this connection the observations by Kleinfeld, Stein, and Magin[13] are of considerable interest. When the oxygen requirement of a single muscle fiber was increased by the administration of triiodothyronine or when oxygen availability was limited by anoxia, electrical alternans occurred. Similarly, Green observed the appearance of pulsus alternans following experimental coronary artery ligation.[14] The relative frequency of pulsus alternans in patients with hypertensive heart disease, in whom total myocardial oxygen requirements are elevated,[15] and in patients with arteriosclerotic heart disease, in whom the oxygen delivery is impaired, is well recognized.

It has recently been demonstrated[16] that the oxygen consumption of the heart is not determined by the external work performed by the heart, but rather by the tension-time index; this is represented by the total area beneath the systolic portion of the ventricular pressure curve per minute. The very close correlation between the product of peak systolic ventricular pressure and heart rate and the tension-time index[16, 17] makes an estimation of the relative myocardial oxygen requirements in clinical conditions readily available (fig. 5). It was therefore of considerable interest to observe that this index of myocardial oxygen requirement (left ventricular systolic pressure times heart rate) correlated so well with the presence or absence of pulsus alternans (fig. 3). Furthermore, it should be noted that in the presence of aortic stenosis, the delivery of oxygen to the myocardium is limited by relatively low coronary perfusion pressure and the prolongation of ventricular systole.[18]

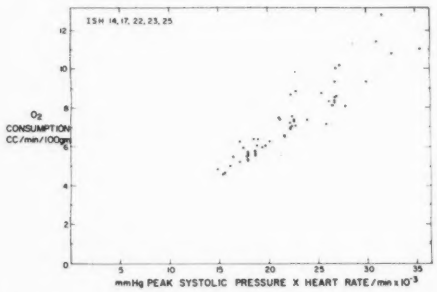

FIG. 5. The relationship between the product of systolic pressure and heart rate and myocardial oxygen consumption per 100 Gm. of heart weight. Fifty observations made on 5 isolated, non-failing dog heart preparations under a wide variety of hemodynamic conditions.[17] These data were obtained by Sarnoff et al. and are reported in detail elsewhere.[16] *(Used by the kind permission of Dr. Stanley J. Sarnoff.*

Review of the data reported by Friedman and associates[19] lends further support to the contention that pulsus alternans is related to changes in myocardial oxygenation. These investigators demonstrated in 3 patients without aortic stenosis that pulsus alternans could be regularly induced by a variety of maneuvers that decreased the venous return, and could be abolished by other maneuvers

that increased venous return. Calculations from their published data indicate that in each instance the development of pulsus alternans was associated with an elevation of the product of arterial pressure and heart rate. This index declined whenever pulsus alternans was abolished.

Although the product of left ventricular systolic pressure and heart rate was high, i.e., exceeded 180×10^2, in 13 of the patients with congenital aortic stenosis, persistent pulsus alternans was never present. This would suggest that in addition to the myocardial oxygen requirement another factor may play a role in the genesis of alternans. The presence of more advanced coronary arteriosclerosis or rheumatic myocardial involvement in the patients with acquired aortic stenosis could explain the observed difference.

The ability to detect pulsus alternans consistently in the peripheral arterial pressure pulse recordings in patients with aortic stenosis enhances the clinical value of the observations reported. Thus, in patients with the clinical picture of aortic stenosis, the presence of pulsus alternans in the brachial arterial tracing suggests a more serious form of the disease. The detection of pulsus alternans in the peripheral pulse tracing is facilitated by the use of high sensitivity recordings at a slow paper speed.

Summary

Fifty patients with aortic stenosis were studied by means of left heart catheterization. Persistent left ventricular pulsus alternans was observed in 15 of 28 patients with acquired aortic stenosis, but in none of 22 patients with congenital aortic stenosis. No consistent relationship could be established between the presence of persistent pulsus alternans in acquired aortic stenosis and age, duration of symptoms, fatigability, syncope, heart rate, or the left ventricular end-diastolic pressure. Those patients with persistent alternans, however, more frequently had severe congestive heart failure, angina pectoris, and cardiomegaly. Furthermore, the left ventricular systolic pressures and the left ventricular-aortic pressure gradients were significantly higher in these patients.

The hemodynamic parameter that afforded the best separation of those patients with acquired aortic stenosis and persistent pulsus alternans from those without alternans, was the product of the left ventricular systolic pressure and the heart rate. This product closely correlates with the tension-time index, which has recently been shown to reflect myocardial oxygen requirement.

These observations, in the light of previously reported data, suggest that a disparity between the oxygen requirement of the heart and the oxygen available to it, can so alter myocardial contractility as to result in alternation in the strength of the ventricular contractions. The absence of alternans in patients with congenital aortic stenosis of similar severity suggests that coronary arteriosclerosis and the sequelae of rheumatic myocarditis may be contributory factors in its genesis.

Summario in Interlingua

Cinquanta patientes con stenosis aortic esseva studiate per medio de catheterismo sinistro-cardiac. Persistente pulso alternante sinistro-ventricular esseva constatate in 15 ex 28 patientes con acquirite stenosis aortic sed in nulle ex 22 patientes con congenite stenosis aortic. Il non esseva possibile establir un relation systematic inter le presentia de persistente pulso alternante in casos de acquirite stenosis aortic e factores como etate, duration del symptomas, fatigabilitate, syncope, frequentia cardiac, e pression sinistro-ventricular termino-diastolic. Tamen, le patientes con persistente pulso alternante habeva plus frequentemente conditiones como grados sever de congestive disfallimento cardiac, angina de pectore, e cardiomegalia. In plus, le pression sinistro-ventricular systolic e le gradiente de pression inter ventriculo sinistre e aorta esseva significativemente plus alte in iste patientes.

Le melior criterio hemodynamic pro le separation del patientes in qui le acquirite stenosis aortic esseva associate con persistente

pulso alternante ab le patientes sin pulso alternante esseva le producto de pression sinistro-ventricular systolic e frequentia cardiac. Iste producto es intimemente correlationate con le indice de tension e tempore le qual—secundo recente constatationes—reflecte le requirimentos oxygenic del myocardio.

Iste observationes, vidite in le lumine de datos previemente reportate—suggere que un disparitate inter le requirimentos de oxygeno del corde e le quantitate de oxygeno disponibile al corde es capace a alterar le contractilitate myocardial in un tal maniera que un alternation resulta in le fortia del contractiones ventricular. Le absentia de pulso alternante in patientes con congenite stenosis aortic de grados comparabile de gravitate pare indicar que arteriosclerosis coronari e le sequellas de myocarditis rheumatic es possibilemente factores contributori in le genese de pulso alternante.

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Nephrogenic Hypertension (Goldblatt Kidney) Following Operative Trauma to the Renal Artery

By RICHARD T. MCDONALD, M.D., D. EMERICK SZILAGYI, M.D., AND ROGER F. SMITH, M.D.

The thrombosis of the right renal artery following operative injury set off a chain of events closely duplicating the arterial hypertension observed by Goldblatt after constriction or occlusion of the renal arteries in experimental animals. The resulting hypertension was severe, fulminating, prolonged, and resistant to treatment by hypotensive and ganglion-blocking agents; it was associated with pulmonary edema, myocardial infarction, and impairment of the renal function. Nephrectomy brought about a return of the blood pressure to normal levels. The concentration of renin in the removed kidney was 34 times greater than normal.

THE pioneer work of Goldblatt on the role of the kidney made ischemic by constriction or occlusion of the renal arteries (with concomitantly patent renal veins) in the development of a type of arterial hypertension has received abundant experimental confirmation.[1, 2] Clinical corroboration of the validity of these observations has likewise been convincing. Numerous case reports attest that certain cases of arterial hypertension are cured by the removal of an ischemic kidney.[3, 4] More recently relief of arterial hypertension has been achieved by surgical correction of atherosclerotic occlusive lesions in the renal artery.[5–7] Insofar as we have have been able to ascertain, however, no instance of a direct human counterpart of the so-called Goldblatt kidney has hitherto been reported. Thus a case observed by us in which thrombosis of the renal artery supervening on surgical trauma resulted in fulminating hypertension seems to have documentary interest.

CASE REPORT

In April 1956, G.S.P., a 59-year-old Caucasian man was referred to the Henry Ford Hospital for the evaluation of an asymptomatic abdominal aneurysm. The past and family history were noncontributory.

Physical examination revealed a well-developed and well-nourished man with temperature of 98.6 F., pulse of 72, and blood pressure of 130/80 mm. Hg. The positive physical findings were limited to the abdomen and consisted of a pulsating midabdominal mass measuring 12 by 8 by 8 cm.

The routine morphologic studies of the blood gave normal results. Urinalysis showed no abnormal findings. The blood urea nitrogen was 11.5 mg. per 100 ml., the 15-minute urinary phenolsulfonphthalein excretion was 21 per cent, the serum creatinine was 0.8 mg. per 100 ml., and the 24-hour creatinine clearance test gave the value of 134.5 ml. per minute. The serology was negative and the electrocardiogram was within normal limits.

A translumbar aortogram on April 3, 1956, with 70 per cent Urokon revealed an aneurysm of the abdominal aorta without involvement of the renal arteries (fig. 1).

The patient deferred surgical treatment until June 14, 1956. There had been no subjective or objective change in the aneurysm. The blood pressure was again normal (110/70), and the basic laboratory work was repeated and found unchanged.

On June 16, 1956, an aneurysmectomy was performed under catheter spinal anesthesia. Exploration of the abdominal viscera was negative except for a 2-cm. clear cyst on the left lobe of the liver and the expected aneurysm. Following the first 30 minutes of the operation an episode of tachycardia occurred, associated with transient hypotension. This was relieved by norepinephrine infusion, and the blood pressure during the rest of the operation ranged from 90/60 to 160/100 mm. Hg.

During the dissection of the anterior surface of the aneurysm, approximately 2 cm. distal to the level of the left renal vein, an artery 5 mm. in diameter was inadvertently incised. This was immediately repaired without incident by means

From the Department of Surgery, Henry Ford Hospital, Detroit, Mich.

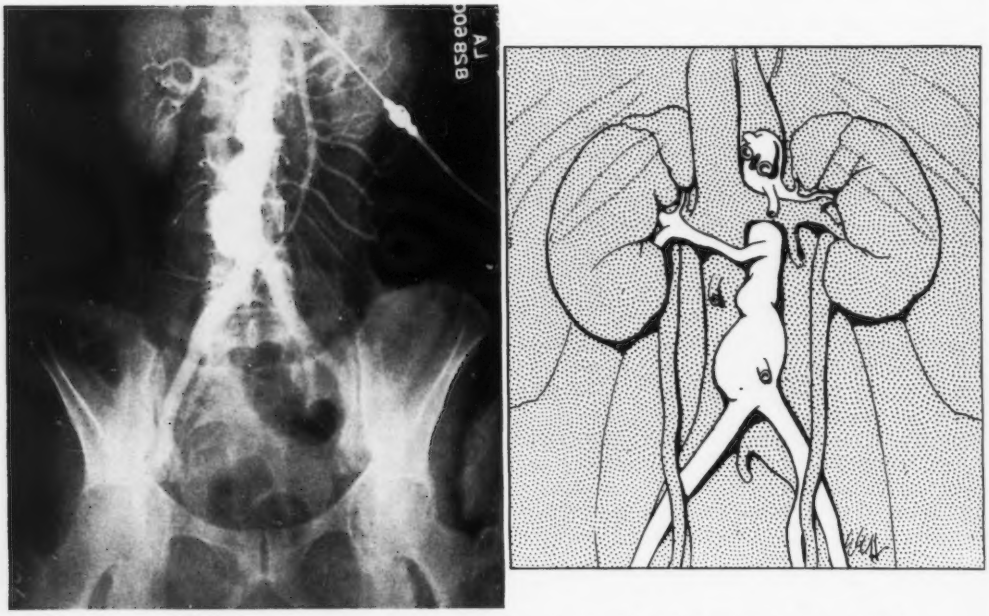

FIG. 1 *Left.* Translumbar aortogram showing an aneurysm of moderate size. *Right.* Artist's sketch of the relationship of the aberrant right main renal artery.

of 3 interrupted 5-0 arterial silk sutures. Further dissection identified this artery to be an aberrant main right renal artery. The aneurysm was then resected and replaced with a fresh aortic homograft. At the close of the operation, the total duration of which was 3 hours, the aberrant right renal artery was pulsating normally.

During the immediate as well as the later postoperative period the patient's recovery was marred only by the abnormal behavior of the blood pressure (fig. 2). The day after operation the blood pressure was found to be 108/70 and during the subsequent 3 days it showed a steady rise, reaching 250/176 on the fourth postoperative day. At this time acute pulmonary edema developed which responded to morphine sulfate, oxygen, aminophylline, and digitalization.

During the subsequent 15 days the cardiac state of the patient bordered on congestive failure and was further worsened by the appearance of a small anterior myocardial infarction on the ninth postoperative day. In an attempt to reduce the blood pressure intramuscular Rauwolfia (reserpine) was started in a daily dosage of 0.5 mg. and increased during the next 4 days to 11.25 mg. The blood pressure was not appreciably altered, remaining at or near 230/140. In order to remedy the acute mental depression brought on by the drug the dosage was decreased to 0.5

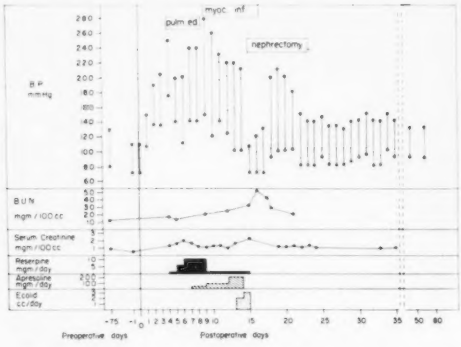

FIG. 2. Chart of the serial blood pressure readings and of the pertinent laboratory data, clinical events, and types of medication.

mg. per day, which was continued until the fifteenth day. On the seventh postoperative day hydralazine hydrochloride (Apresoline) was started in a daily dose of 40 mg. and was increased stepwise to a total of 200 mg. a day; on the twelfth postoperative day it was discontinued because of its ineffectiveness, the blood pressure having stayed around 220/126. Chlorisondamine chloride (Ecolid) 2 ml. per day was begun but terminated in 2 days at a level of 3 ml. per day. The total

FIG. 3 *Top.* Photograph of the removed kidney. The combined area of the infarcts was about 30 per cent of the whole cut surface. (Occluding thrombus from the renal artery on the right.) *Bottom.* Cut surface of kidney demonstrating the depth of the infarctions.

reduction of the blood pressure by means of these tried antihypertensive agents was slight; the west blood pressure level obtained was 210/100. By the fifteenth postoperative day the indications for surgical intervention for the correction of the hypertension had become pressing. The use of antihypertensive drugs had been fruitless; the patient's cardiac status, under the strain of the elevated blood pressure, had remained precarious; and intravenous pyelograms showed the right kidney to be functionless. On the fifteenth postoperative day through a right subcostal incision the right kidney was explored. The operative plan was to attempt a repair of the right renal artery if at all possible and salvage the kidney. This, however, did not prove feasible. The entire main trunk of the renal artery was solidly thrombosed. A nephrectomy was therefore performed. It should be mentioned that there was no accessory renal artery and the right renal vein was patent.

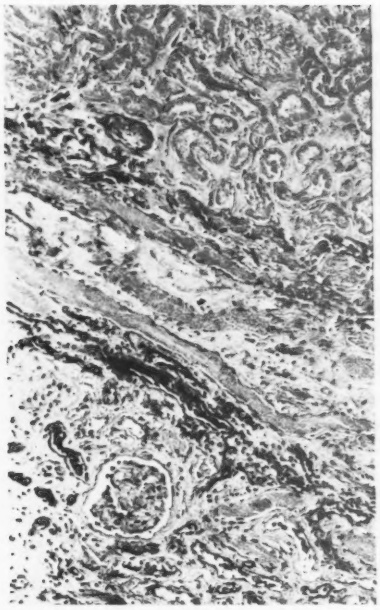

FIG. 4. Photomicrograph of a section of the renal cortex near the border of an infarct. Necrotic glomerular and tubular elements on top, with degenerative changes and edema in a probably still viable area on bottom. × 125.

At the end of the operation the blood pressure was 120/72. Moderate hypotension then developed and the blood pressure had to be maintained at 120 (systolic) by an infusion of 4 mg. of norepinephrine diluted in 1 liter of 5 per cent dextrose in water.

During the next 2 days the patient required methoxamine hydrochloride (Vasoxyl) intramuscularly in 10 mg. doses every 6 hours to maintain his systolic blood pressure between 120 and 130. Two hundred milligrams of hydrocortisone daily was given for 2 days intravenously on an empirical basis without apparent effect. On the third day after the nephrectomy, the blood pressure again was recorded as 200/90. This or a similar level persisted for 3 more days. The blood pressure then fell spontaneously and gradually, and ranged from 150/100 to 130/80 (with the lower pressures

predominating) until the patient's discharge 20 days later. Blood pressure readings 2, 3, and 12 months after nephrectomy were consistently near 130/80 or lower. The patient at the present time is carrying on a full university teaching schedule.

Pathologic Examination of Surgical Specimen. The removed kidney was, as a whole, pale grayish pink, soft, and slightly enlarged. (Through oversight, the weight of the organ was not recorded.) About 30 per cent of the cortical surface was covered with scattered irregular elevated areas of dark reddish color (fig. 3 *Top*). The darker discoloration was seen on the cut surface to extend into the underlying medullary substance (fig. 3 *Bottom*). The pelvis and the calyces were not dilated. The thrombus in the renal artery completely occluded the lumen and measured 1 by 0.4 cm. In the microscopic sections large areas of ischemic necrosis involving all parenchymatous elements were present, interspersed with zones of tissue that showed only edema and some tubular necrosis. No changes of arteriolar nephrosclerosis were seen (fig. 4).

Half of the kidney was submitted to Dr. George Wakerlin (Department of Physiology, University of Chicago) for an assay of its renin content. The renin content was 3.4 dog units per Gm., a striking increase over the normal value of 0.1 unit per Gm.

Discussion

On viewing the events of this case as the postoperative picture unfolded, we gained the impression that we were dealing with a phenomenon best explained by the well-known mechanism of pathogenesis of hypertension extensively studied and described by Goldblatt. What evidence is there that this impression is correct?

The first proof one can place in evidence is the temporal relationship of the events. The appearance of a rapidly progressing malignant hypertension following surgical trauma to the renal artery in a patient who had been known to be normotensive for years had by common logic to be causatively linked with the event of trauma. At the time of the second surgical intervention the causal connection was further strengthened by the confirmation of the presence of an occluding thrombus in the renal artery, by the extensive but far from complete ischemic necrosis of the renal parenchyma, and by the relief of the hypertension by the nephrectomy. The conclusive proof of the pathogenetic relationship was the demonstration of the markedly increased content of renin in the parenchyma of the involved kidney. As will be recalled, the sequence of events terminating in hypertension is set in motion by the ischemic kidney through the production of *renin* which, by reacting with the blood *hypertensinogen*, results in the appearance of the active vasoconstrictive principle *hypertensin*. Thus the clinical episodes of this case as well as the pathologic findings and the bioassay of the renal tissue support the view that the kidney with its accidentally impaired blood supply was a counterpart of the Goldblatt experimental preparation producing arterial hypertension.

Some details of the case deserve comment. The temporary hypotension rapidly supervening on the removal of the kidney was at first puzzling. It can, however, be explained by the summation of the effects of the removal of the pressor agent and the persistence of response to the large preoperative doses of antihypertensive drugs. While the survival of part of the parenchyma of the kidney is essential for the production of renin, the large proportion of the kidney that in this case was relatively unaffected was surprising. Neither the preoperative aortogram, which was of good quality, nor the operative dissection revealed an accessory renal artery. The operative dissection was not thorough enough, however, to exclude with certainty the presence of an accessory vessel. Nevertheless, the probability of the existence of such a vessel was very small, and one is obliged to assume that the auxiliary blood supply came through capsular branches.

No plausible explanation can be afforded for the temporary and relatively mild hypertension that appeared 3 days after nephrectomy and disappeared in 4 days by stepwise decrements. In the reported cases of nephrectomy for hypertension of nephrogenic origin the return of the blood pressure to a normal level, if it took place at all, was prompt. The anatomic background for these cases, however, is significantly dissimilar

from that in the case reported. Interestingly enough, however, in a case described by Boeminghaus,[8] in which the postoperative hypertension was the result of renal ischemia following the ligation of an accessory renal artery (a situation more nearly comparable to that in our case) a temporary persistence of hypertension was likewise noted.

In passing it may be mentioned that the variability of the response of the renal parenchyma to a reduction of its main blood supply through the renal artery may well be due to the differences in the pattern and extent of the capsular arteries that constitute a potentially important collateral arterial bed.

Summary

A report is given of an instance of malignant arterial hypertension supervening on inadvertent surgical trauma and eventual thrombosis of the right renal artery, and cured by right nephrectomy. The sequence of clinical events, the pathologic findings, and the bioassay of the parenchyma of the removed kidney are interpreted as proofs that the hypertension in this case was a clinical counterpart of the experimental hypertension produced under certain conditions by the constriction or occlusion of the renal artery.

Summario in Interlingua

Es reportate un caso de maligne hypertension arterial, superveniente post trauma chirurgic accidental sequite—in le curso del tempore—per thrombos e del arteria dextero-renal. Curation del patiente esseva effectuate gratias a nephrectomia dextere. Le sequentia del evenimentos clinic, le constatationes pathologic, e le bio-essayage del parenchyma del ren excidite es interpretate como provas que le hypertension in iste caso esseva un correspondentia clinic del hypertension experimental producite sub certe conditiones per le constriction o le occlusion del arteria renal.

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Erratum

On page 856, of the May 1958 issue, (article by Friedman et al.) the legends for figures 2 and 3 should be transposed.

Clearing Factor Inhibitor in Human Atherosclerosis

By ALLAN J. DAY, M.D., M.Sc., AND GRAHAM N. WILKINSON, M.Sc.

With the technical assistance of J. A. Peters, D.M.T.

A reduction in heparin-activated clearing factor has been demonstrated in individuals with atherosclerosis or conditions related to it. The recent isolation from normal plasma of an inhibitor to clearing factor suggested that the reduction described might be due to an increased level of inhibitor. This possibility was therefore investigated by determining the inhibitor effect of the plasma of atherosclerotic, diabetic, and nephrotic individuals on the in vitro clearing activity of post-heparin plasma.

THE role of heparin in the pathogenesis of human atherosclerosis still requires considerable clarification. The fact that heparin is capable of altering the blood lipid picture,[1-4] and that atherosclerosis is associated with increased blood lipid levels,[5-7] naturally directed investigation to heparin deficiency as a contributing factor. It has been reported that the blood heparinoids are reduced in atherosclerotic subjects[8, 9] and also that heparin administered therapeutically exerts a favorable influence on persons with coronary atheroma.[10, 11] Heparin, however, does not act directly on blood lipids, its action being brought about by the elaboration of clearing factor,[12] which is capable of clearing fat emulsions both in vivo and in vitro. It has been shown that the elaboration of clearing factor is reduced in individuals with atherosclerosis,[13, 14] small doses of intravenous heparin producing less clearing following a fat meal in this group. The evidence that clearing factor is present in normal plasma[15, 16] and can be extracted from normal tissues,[17] increases in importance any possible disturbance of the clearing reaction manifested by the atherosclerotic individual. Disturbance of the physiology of fat transport resulting from a reduced clearing rate may therefore be a factor in the elevated lipid levels of the atherosclerotic individual. Further, in experimental nephrosis and diabetes,[18, 19] there is evidence of a reduced clearing factor response to heparin and both these conditions are well known precursors of atherosclerosis.

Recently it was found[20, 21] that normal plasma contained a substance, probably a glycoprotein, capable of inhibiting clearing factor. The decreased clearing following small doses of heparin in older persons and atherosclerotic subjects in particular,[13, 14] could well be related to a higher level of inhibitor in these groups. The possibility of an increased level of clearing factor inhibitor in individuals with atherosclerosis and related conditions was therefore considered worth investigating. Indeed recently Klein and Lever[22] reported that idiopathic hyperlipemia was associated with increased clearing factor inhibitor activity and Angervall and Hood[20, 23] made some inconclusive observations on its presence in atherosclerotic subjects.

In this paper the clearing factor inhibitor activity of the plasma of atherosclerotic, diabetic, and nephrotic subjects is determined and compared with that of younger student controls and with controls of equivalent age.

METHODS

The plasma of 4 groups of individuals were investigated for their clearing factor inhibitor activity. The control group consisted of 16 normal medical students varying in age from 19 to 27 years (mean = 22.0). The second group was an older control group consisting of 14 subjects varying in age from 35 to 72 years (mean = 48.5). They were mostly convalescent hospital patients with no evidence of atherosclerosis or related conditions. The third group consisted of 17 individuals of equivalent age, but with definite evidence of coronary atherosclerosis. They were either patients with a history of myocardial infarction, at least 3 months before, or of severe angina pectoris. Their age varied from 40 to 72 years (mean

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TABLE 1.—*In vitro, Clearing Rate (k) of Post-Heparin Plasma When Mixed with Untreated Plasma (Student, Age Control, Atherosclerotic, Diabetic, and Nephrotic)*

Date	Student		Age control		Atherosclerotic		Diabetic		Nephrotic	
	Age	k	Age	k	Age	k	Age	k	Age	k
19/8	26	.123	—	——	53	.172	68	.078	—	——
	26	.122	—	——	—	——	80	.095	—	——
10/9	19	.143	40	.090	46	.062	63	.192	48	.115
	27	.153	—	——	—	——	52	.143	—	——
16/9 (1)	24	.168	49	.138	49	.138	51	.182	46	.140
16/9 (2)	23	.171	39	.098	40	.102	—	——	—	——
	—	——	72	.105	—	——	—	——	—	——
23/9 (1)	22	.168	65	.160	60	.152	—	——	—	——
	—	——	—	——	72	.118	—	——	—	——
23/9 (2)	21	.165	40	.132	—	——	—	——	—	——
	—	——	50	.147	—	——	——	——	—	——
24/9	20	.158	37	.140	53	.115	—	——	—	——
30/9 (1)	21	.114	70	.130	48	.092	—	——	—	——
	—	——	—	——	58	.158	—	——	—	——
30/9 (2)	22	.100	—	——	55	.082	—	——	—	——
	—	——	—	——	58	.120	—	——	—	——
8/10 (1)	20	.180	41	.220	53	.162	26	.180	—	——
	—	——	—	——	—	——	74	.135	—	——
	—	——	—	——	—	——	17	.180	—	——
8/10 (2)	20	.270	56	.130	66	.240	46	.093	—	——
	—	——	—	——	—	——	67	.240	—	——
8/10 (3)	20	.145	49	.154	55	.140	30	.193	—	——
	—	——	—	——	—	——	58	.160	—	——
21/10 (1)	20	.310	37	.255	67	.213	—	——	—	——
	—	——	—	——	50	.204	—	——	—	——
21/10 (2)	21	.330	35	.325	40	.244	—	——	—	——

= 54.3). The fourth group consisted of diabetic subjects covering a fairly large age range (17 to 80 years). In addition 2 patients with nephrotic syndrome were investigated. Blood was collected from all these individuals into chilled oxalated tubes, and the plasma was separated and kept at 4 C. until the clearing factor inhibitor activity was tested. This was done within 4 hours of collection.

The source of lipemia-clearing factor used for the inhibitor studies was plasma taken from normal medical students after they were given heparin. On each day 1 or more students was given intravenously 1,000 units of heparin and 15 minutes later 10 ml. of blood were removed. It was placed in chilled oxalated tubes and the plasma was separated and kept at 4 C. until used later the same day. Since this procedure was repeated on each day, a different source of clearing factor was used on different days. In order to determine inhibitor activity 0.25 ml. of the active post-heparin plasma was mixed with 0.25 ml. of the plasma to be tested and the resulting clearing activity was determined. The student controls were tested at the same time and under the same conditions as the other 3 groups, as far as possible a representative of all groups being incorporated

TABLE 2.—*Reduction in "in vitro" Clearing Rate Caused by Age Control, Atherosclerotic and Diabetic Plasma Relative to the Student Control in Each Series. Relative Inhibitor Activity Expressed as* $\frac{k(student) - k(test\ group)}{k(student)}$

Age control	Atherosclerotic	Diabetic†
39.2	−39.8*	36.6
17.9	58.0	22.8
42.7	17.9	−29.7*
38.6	40.3	3.4
4.8	9.5	− 8.3*
20.0	29.8	25.0
10.9	27.2	65.6
11.4	19.3	11.1
−14.0*	−38.6*	−10.3*
−22.2*	18.0	—
51.8	−20.0*	—
− 6.2*	10.0	—
17.7	11.1	—
1.5	3.4	—
—	31.2	—
—	34.2	—
—	26.0	—
15.3 ±5.7	14.0 ±6.3	12.9 ±8.9

* Greater clearing rate than respective student controls expressed as negative inhibition.

† Only diabetic subjects over 35 years included.

in the series for each day. It was thus possible on each day or within each series (where 2 sources of clearing factor were used) to compare the amount of inhibition produced by the student control with that produced by the other patients. Thus the clearing factor inhibitor activity of the control, atherosclerotic, and diabetic groups could be compared with the student control.

Lipemia-clearing factor inhibitor activity. The clearing factor activity of the mixture of active post-heparin plasma with the plasma to be investigated was determined by the method of Grossman[24] as modified by Day and Peters.[25] In vitro reduction in the turbidity of the artificial emulsion, when mixed with the plasma mixture, was read immediately after mixing and at 5, 10, 20, 30, 45, and 60 minutes thereafter.

The graph of $\log_e D$ (optical density) against time was approximately linear in all cases, indicating that the rate of clearing at any instant was proportional to the optical density at that instant, or in other words that the optical density decreased with time according to the negative exponential decay law. Mathematically, this may be expressed as follows:

$$D_t = D_o\, e^{-kt}$$

$$\frac{dD_t}{dt} = -k\, D_o\, e^{-kt}$$

$$\frac{1}{D_t}\,\frac{dD_t}{dt} = \frac{d}{dt}(\log_e D_t) = -k,$$

where D_t is the optical density at time t (D_o at $t = O$). The constant k is the proportional clearing rate, and is the appropriate index of clearing factor activity.

The k— values were determined in each case by plotting $\log_e D$ against t, fitting a straight line to the plot, and measuring the slope of the line. For comparison of the k— value for a test individual (age control, atherosclerotic etc.) with that for a student, the following index was considered to be more appropriate than the simple difference of k values, namely:

$$I = \frac{k(student) - k\ (test)}{k\ (student)} \times 100\%$$

since it was found that the difference $k_s - k_t$ depended to some extent on the clearing factor activity of the serum used, as indicated by the k value. This index was taken as a measure of clearing factor inhibitor activity in the test individual (relative to control).

RESULTS

Table 1 gives the in vitro clearing rate (k) of post-heparin plasma when mixed with untreated plasma from students, age control, atherosclerotic, diabetic, and nephrotic subjects. On each day, (or in each series if more than one series was performed on the day) the same source of clearing factor was used and the student inhibitor activity was determined at the same time and under the same conditions as the other patients studied on that day. It was possible therefore to consider the student control as having zero inhibitor activity and to relate the inhibitor activity of the test subjects to their respective student control on this basis. In table 2 this has been done and the relative inhibitor activities (I) of the age control, atherosclerotic, and diabetic subjects have been calculated and compared.

It is apparent from tables 1 and 2 that there is greater clearing factor inhibitor activity in all 3 test groups than in the student group. In the age control series, 11 of the 14 subjects have more inhibitor activity than their respective student controls. In the remaining 3 the "negative inhibition" is simply an expression of greater inhibitor activity in the student than in that age control. The mean for I, with its estimated standard error, is 15.3 ± 5.7, an increased

inhibitor activity with age that is statistically significant ($p < 0.02$).

In the atherosclerotic group 14 of the 17 patients demonstrated more inhibitor activity than the respective student controls. The mean value for I for this group was 14.0 ± 3, this difference again being statistically significant ($p < 0.05$). When the atherosclerotic group was compared with the age control group, i.e., with normal individuals of similar age, no significant difference in inhibitor activity was detected. It would seem that the difference in inhibitor activity between the student and atherosclerotic groups may be explicable entirely on an age basis and not related to atherosclerosis as such.

In the diabetic group, when the younger diabetics (< 35 years) are excluded, the mean inhibitor activity (I) is 12.9 ± 8.9. Because of the large variance this value is not significantly different from the student group, but it is of the same order as the other 2 "older groups." No significant difference in inhibitor activity exists between the diabetic and the age control or atherosclerotic individuals. Thus no specific increase in inhibitor activity can be attributed to the diabetic state. It is worth noting that in the 3 younger diabetics (26, 17, and 30 years) the inhibitor activity is of the same order as the student controls. Thus when the age factor is eliminated, the increased inhibitor activity in this group is also eliminated.

Definite conclusions cannot be drawn about the 2 nephrotic subjects, but it is interesting that there is inhibitor activity (compared with the student control) in both. However this inhibition is similar in magnitude to that of the age controls investigated on the same day and can therefore be accounted for purely on an age basis.

Discussion

It has been found that the plasma of older individuals inhibits lipemia-clearing factor to a greater degree than younger controls. This elevated inhibitor activity with aging is in accord with the recent findings of Nikkilä and Niemi,[26] who have shown heparin to produce less clearing factor in older subjects than in younger controls. The presence of more inhibitor activity as shown here would reduce the post-heparin clearing activity and thus account for this apparently reduced response. In a previous communication[4] we have recorded the fact that protamine elevates the serum total fatty acids in normal students, but has no effect in older age groups. This was interpreted to indicate a deficiency in circulating heparin produced with aging. Hollett and Meng[27] have shown that protamine is capable of inhibiting clearing factor and that its action on lipids may be related partly to this inhibition. The changing response with age of fatty acids to protamine could therefore also be explained in terms of an increased clearing factor inhibitor activity. With the small amount of normal clearing factor already inhibited in the older age groups, the inhibiting effect of protamine would not be able to manifest itself and minimal changes would result. The reduced fat tolerance with increasing age[28, 29] can also be related to the increased inhibitor level. Clearing factor, physiologically concerned with lipid removal following a fat meal, is prevented from adequately doing so by the increased inhibitor activity and the fat level is able to rise to a higher level in the older age groups. The findings of Block, Barker, and Mann[13] that a reduced sensitivity to heparin exists in atherosclerotic individuals can also be interpreted in terms of the findings of this present paper. In actual fact these workers used a very much younger control group and the reduced clearing by heparin, attributed by them to atherosclerosis, was possibly no more than an age difference. Such an age difference probably relates to an increased inhibitor level and not to a reduced sensitivity to heparin as was supposed. The difference due to atherosclerosis, although supported by Oliver and Boyd,[14] was not confirmed by others.[30, 31]

Whether there is a difference in clearing factor inhibitor activity specific to individuals with atherosclerosis is doubtful. Certainly no evidence to that effect was obtained here. It is relevant to raise the difficulty in selection of nonatheromatous controls, the problem of satisfactorily excluding individu-

als with occult atheroma being widely appreciated. Nevertheless Angervall and Hood,[20, 23] while obtaining some evidence for increased inhibitor activity with atheroma, were unable to confirm this and they concluded that no real difference exists. The possibility remains however, that one influence of aging on the atherosclerotic process is the demonstrated increase in clearing factor inhibitor with its consequent effect on blood lipid level.

Regarding the inhibitor activity of the diabetic and nephrotic groups, little further need be said. No difference specific to the respective conditions was noted, the only change being one associated with the age of the individual and similar in magnitude to the age control group.

Summary

The inhibitor effect of the plasma of atherosclerotic, diabetic, and nephrotic individuals on in vitro clearing activity of post-heparin plasma was determined and compared with that of student controls and older controls. A significant increase in inhibitor activity was shown to exist between the older control group and the student group. A similar increase in inhibitor activity was demonstrated when the atherosclerotic group was compared with the student group, but no difference existed when compared with the control group of similar age. An increase in inhibitor activity was found in both the diabetic and nephrotic group, but again no difference when the age effect was eliminated. It was considered that an increased level of clearing factor inhibitor results from aging, but that no increased activity occurred with atherosclerosis, diabetes, or nephrosis, other than that accountable for by age.

Acknowledgment

We are indebted to Dr. H. R. Gilmore of the Department of Medicine for the selection of much of the clinical material and for the consequent blood sampling. To Mr. A. E. Bowey of the Department of Pharmacy for preparing the emulsion substrate used for clearing factor determinations, to Miss M. Redway for technical assistance, and to the many students and patients who cooperated in this investigation we would also like to record our thanks.

Summario in Interlingua

Esseva determinate le effecto inhibitori qu plasma ab individuos atherosclerotic, dia betic, e nephrotic exerce in vitro super le ac tivitate clarificatori in plasma post-heparinic Le resultatos esseva comparate con le corre spondente effecto exercite per plasma al individuos de controlo (1) de etate universi tari e (2) de etate plus avantiate. Esseva constatate un augmento significative in le ac tivitate inhibitori in le caso del gruppo d controlo a etate avantiate in comparation co le gruppo de studentes universitari. U simile augmento del activitate inhibitor esseva demonstrate in le caso del grupp atherosclerotic in comparation con le grupp de studentes, sed nulle differentia existeva inter le gruppo atherosclerotic e un grupp de controlo de simile etates. Esseva consta tate un augmento del activitate inhibitori i le gruppo diabetic e etiam in le gruppo neph rotic, sed etiam in iste caso le differentia dis pareva si tosto que le effecto del etate esseva eliminate. Es formulate le opinion que u augmento del activitate del factor clarificatori resulta ab le avantiamento del etate sed que nulle tal augmento occurre in casos de athe rosclerosis, de diabete, o de nephrosis, excepte le augmento que es explicabile per le etate del subjectos.

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Movements and Forces of the Human Heart

V. Precordial Movements in Relation to Atrial Contraction

By T. R. Harrison, M.D., John A. Lowder, M.D., Lloyd L. Hefner, M.D., and Donald C. Harrison, M.D.

Precordial movements starting after P and before Q have been studied. Right atrial contraction appears to cause a forward-rightward motion and left atrial contraction a backward movement of the precordium. The latter is exaggerated in most patients with mitral stenosis and in some patients with myocardial failure.

STUDY of records of precordial movements of certain patients with cardiac disease has indicated that motions beginning after the P wave and before the Q of the electrocardiogram are sometimes strikingly exaggerated. An understanding of these abnormal motions can only be achieved if one can first interpret the significance of the smaller movements occurring in normal subjects at this time. This communication represents an attempt at such an interpretation.

Methods

Ninety-nine subjects were studied. They were divided into 6 groups, as follows: (1) 22 healthy adult males aged 21 to 39; (2) 3 subjects with varying degrees of heart block; (3) 30 patients with mitral stenosis and sinus rhythm; (4) 10 persons with "pure" mitral insufficiency; (5) 7 patients with cor pulmonale; (6) a miscellaneous group of 27 consecutive subjects with sinus rhythm and various other types of acquired cardiac disease.

Tracings of precordial motions (kinetocardiograms) were obtained either by the crossbar-bellows technic previously described,[1] or by using a bellows in the center of the funnel, with a terminal cross-sectional diameter of 11 cm. In a few instances a tripod was used rather than the funnel. The results obtained by the different technics were similar. All recordings were made with a 4-channel Sanborn Direct Writer, the electrocardiogram and carotid pulse curves being used for reference.

Most of the traces were taken while the breath was held at the end of normal expiration. In a number of subjects records were made during normal breathing. However, the large respiratory excursion of the chest tended to obscure the smaller circulatory motions.

Tracings were taken from the right and left parasternal regions in the fourth interspace (K_{14} and K_{24} areas), and from the left midclavicular line in the fifth interspace (K_{45} area). In a number of subjects the precordium was "mapped" by taking multiple records from the second to the sixth interspace in the 2 parasternal and in the left midclavicular lines. It was found that these extensive recordings yielded little additional information, and therefore in most of the subjects only records from the K_{14}, K_{24} and K_{45} points were analyzed in detail.

In labeling the tracings the letter K indicates "kinetocardiogram;" the first numeral in the subscript refers to the V position, and the second to the interspace. Thus K_{14} is the record from the right parasternal line in the fourth interspace, K_{45} the left midclavicular line in the fifth interspace, etc.

In the analysis of the records a movement was considered to be of atrial origin only if it started after the onset of the P wave of the electrocardiogram, and either before or within .02 second after the start of the QRS complex. In subjects with rapid heart rates there were often large waves just prior to the P wave, which were probably related to passive ventricular filling (fig. 1*B*). Individuals with slow rates often displayed very small motions before the P wave, the cause of these being unknown.

The directions of movement were studied, an upstroke representing an outward motion and a downstroke an inward motion. The time of onset of a given movement in relation to the beginning of the P wave was measured. Since we have no entirely satisfactory method of calibrating the absolute magnitude of precordial movements, as yet, only relative magnitude could be studied. Such relative magnitudes were expressed as the number of millimeters deflection of a given motion

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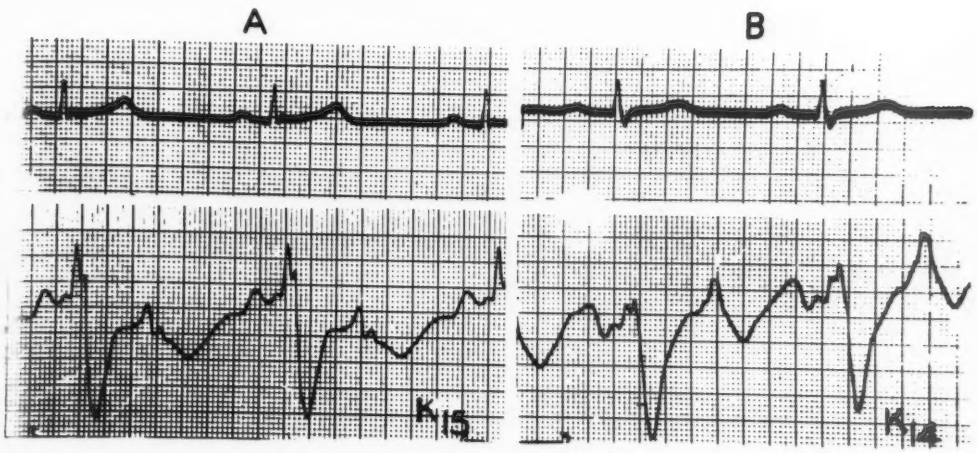

FIG. 1. Normal males. Paper speed, 50 mm. per second. The records were taken in the right parasternal line in the fifth (*A*) and fourth (*B*) interspaces. In a given subject the records of atrial motion from these 2 interspaces are practically identical.

Both subjects display an initial upstroke (outward motion) beginning .04 to .06 second after the onset of P. This motion is relatively larger and more clearly defined in *A* than in *B*. In the second complex of *B* this atrial motion is superimposed on the preceding upstroke of ventricular filling, and its onset is not clearly defined. The relative magnitudes of this upstroke, i.e., the excursion as compared to the differences between the highest and lowest points of the entire cardiac cycle, are 5/33 and 5/34 in *A*, and 2/31 in *B*. The maximal value thus far found in normal subjects for the upstroke is one fourth of the magnitude of the ventricular excursion.

Both subjects display a downstroke beginning .09 to .10 second after the start of the P wave. This downstroke is smaller than the preceding upstroke in *A*, but larger in *B*. The relative magnitude in relation to the highest and lowest points of the ventricular complex is about one thirteenth in *A* and one fifth in *B*. In normal subjects the downstroke does not appear to exceed one third of the maximal ventricular excursion.

There is a small upstroke starting .02 to 0 second before the beginning of the QRS in both subjects. This movement is soon followed by larger and abrupt motions that are obviously of ventricular origin.

The 3 movements mentioned above are believed to be related to (1) right atrial contraction; (2) left atrial contraction (and possibly right atrial relaxation); and (3) left atrial relaxation.

A very small downstroke starting .01 to .03 second after Q is seen in both subjects. It is uncertain whether this movement is of atrial or ventricular origin.

in relation to the greatest total deflection during the cardiac cycle. Thus an increase in relative magnitude might be the result of augmented atrial motion or of diminished ventricular motion.

After these studies had been completed, it was deemed desirable to investigate the lateral movements in relation to atrial contraction. Therefore, ballistocardiograms were recorded (with the cross-bed technic[1]) on 10 normal young adult males, using multiple interspaces in each midaxillary line. The records from the fifth and sixth interspaces were selected for study because they displayed the least variability. Lateral ballistocardiograms, as determined by the low-frequency acceleration technic used in this laboratory,[2] were also analyzed. Lateral motions have not yet been studied in patients with cardiac disease. Longitudinal ballistocardiograms were also recorded but are not discussed because they yielded inconsistent results during this portion of the cardiac cycle.

RESULTS

The more pertinent findings are illustrated in figures 1 to 5, and the data are summarized in the tables.

A. *Anteroposterior movements.*

The normal magnitude of atrial motion in relation to the largest excursion of the cycle is illustrated in figure 1. It may be noted that the 2 subjects, although displaying con-

TABLE 1.—*Relative Amplitude of K_1 Atrial Precordial Motions in Patients with Various Types of Heart Disease*

Group	Number of records	Initial upstroke greater than			Initial downstroke greater than		
		1:4	1:3	1:2	1:4	1:3	1:2
Normal	22	0	0	0	1	0	0
Mitral stenosis	30	5	2	0	27	18	7
Mitral insufficiency	10	2	1	0	7	3	0
Cor pulmonale	7	5	4	1	1	1	1
Myocardial infarction, old	10	3	2	0	9	6	1
Angina pectoris	5	3	2	0	4	1	0
Hypertension	5	2	1	0	4	2	1
Aortic insufficiency	5	2	1	0	0	0	0
Myocarditis (?)	2	2	1	0	0	0	0

siderable difference in magnitude of the different motions, exhibited similarity in configuration of the movements starting after the P wave and before the QRS. During this period all the normal subjects exhibited 3 successive movements, consisting of an initial upstroke (forward), followed by a downstroke (backward), and a second terminal upstroke (forward). Since there is reason to believe that these 3 motions represent different forces, they may now be considered separately.

1. *Initial Forward Movements.* This motion was present in the right parasternal (K_1) region in each of the normal subjects, but was less constant in the left parasternal (K_2) and left midclavicular (K_4) areas. The motion was usually larger at the K_1 region than at the other points. In some instances this upstroke consisted only of an abrupt cessation of a previous downstroke; in others, it represented a change in slope of a previous more gradual forward motion. The time of onset of this forward motion was relatively constant, being .05 ± .03 second after the onset of the P wave. The relative magnitude was small, varying from one twentieth to one fourth of the total excursion of the cycle, and averaged about one eighth. In no normal subject was this movement larger than 25 per cent of the total amplitude of the cardiac cycle (table 1).

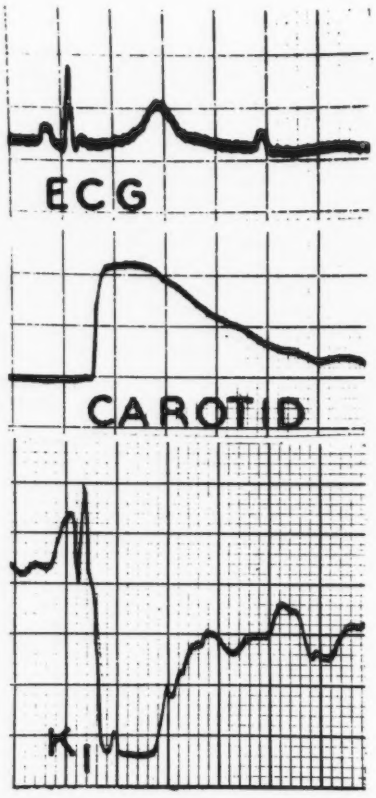

FIG. 2. Complete heart block. Paper speed 25 mm. per second. Following the first P wave there is an initial upstroke but the subsequent atrial events are masked by ventricular forces. After the second P wave, which is not followed by ventricular excitation, the kinetocardiogram displays (1) forward motion; (2) a diphasic backward movement; (3) a small up-down notch; and (4) a second forward motion. The initial forward movement is ascribed to contraction of the right atrium, the backward motion to contraction of the left and relaxation of the right, and the terminal upstroke to left atrial relaxation. The magnitude of excursion of the atrial motions is less than one fourth that of the ventricular forces. The cause of the small up-down notch that precedes the terminal forward movement is uncertain.

This initial forward movement was present after isolated P waves in each of the 3 subjects with heart block (fig. 2), but displayed considerable variation in 30 records obtained from 27 patients with mitral stenosis. At the K_1 area in the latter subjects, the initial up-

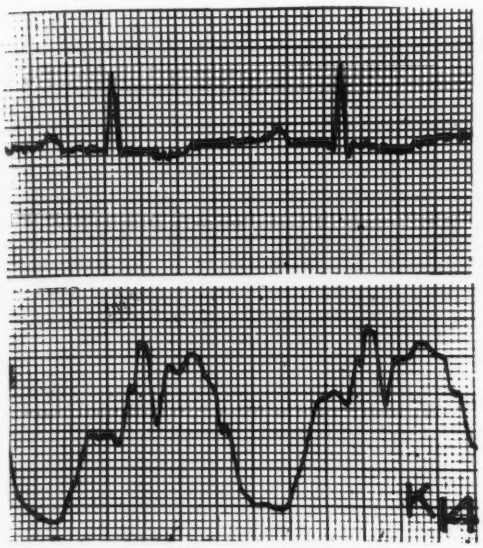

FIG. 3. Cor pulmonale. Paper speed 50 mm. per second. Note the large upstroke starting approximately .05 second after the beginning of the P wave. This is 50 to 60 per cent of the total excursion of the complex. In normal subjects this upstroke, which is ascribed to right atrial contraction, is not more than one fourth of the total deflection. The downstroke ascribed to left atrial contraction is relatively small. In most healthy subjects this downstroke is as large as the preceding upstroke.

stroke was exaggerated (greater than one fourth of the total excursion of the cycle) in 8 instances, was absent in 7 records, and of a magnitude within the normal range in the remaining records. Consistent differences from the normal tracings were likewise not found in the K_2 and K_4 regions of the patients with mitral stenosis.

Two of the subjects with mitral insufficiency displayed exaggeration (greater than 25 per cent) of the relative magnitude of the initial forward motion. In the remainder, the amplitude was within the range of normal.

The most interesting variation was found in the subjects with cor pulmonale. Five of these 7 patients displayed larger relative amplitude than was seen in any of the 22 normal subjects (fig. 3 and table 1).

In 12 of the 27 subjects with other types of cardiac disease, the initial atrial forward motion was exaggerated in relative magnitude. Whether this was the result of an actual increase in the atrial force or of an apparent increase relative to diminished ventricular excursion is uncertain at present.

2. *Initial Backward Motion.* In normal subjects this was the most constant movement, being present at the K_1 point in all of the individuals, and at the K_2 and K_4 areas in nine tenths of the records. The onset was latest and least variable (.11 ± .04 second after P) at the K_1 area (fig. 1), and occurred earliest at K_4 (.07 ± .06 second after P). The values in the K_2 region were intermediate. The relative magnitude of this downstroke at the different areas varied in different subjects. In none of the healthy individuals was the relative magnitude at the K_1 area greater than one third of the total excursion, and in 21 of 22 subjects it was one fourth or less (table 1).

The 3 subjects with heart block all displayed this downstroke, and in each of them it was noted to be biphasic (fig. 2). This biphasic feature was only occasionally noted in normal subjects, or in patients with other types of cardiac disease.

Individuals with mitral stenosis exhibited exaggeration of this backward motion (fig. 4*A* and *C*). It was present at K_1 and K_2 in all such subjects, but was occasionally absent in the K_4 region. This backward motion was absent during atrial fibrillation (fig. 4*B*). At the K_1 region this movement was greater in 27 of the 30 records from patients with mitral stenosis than in any of the normal subjects (table 1). The average magnitude was also greater at the K_2 and K_4 points, but was outside the normal range only in about one half of the records obtained from these regions.

Seven of the 10 patients with mitral insufficiency, and 1 of the 7 patients with cor pulmonale, exhibited increase in the relative amplitude of this backward motion in the right parasternal area. The magnitude was likewise increased in 17 of the 27 patients with other types of cardiac disease (table 1). As in the case of the preceding forward movement, it is uncertain whether the atrial motion was actually increased or whether the ventricular excursion was diminished.

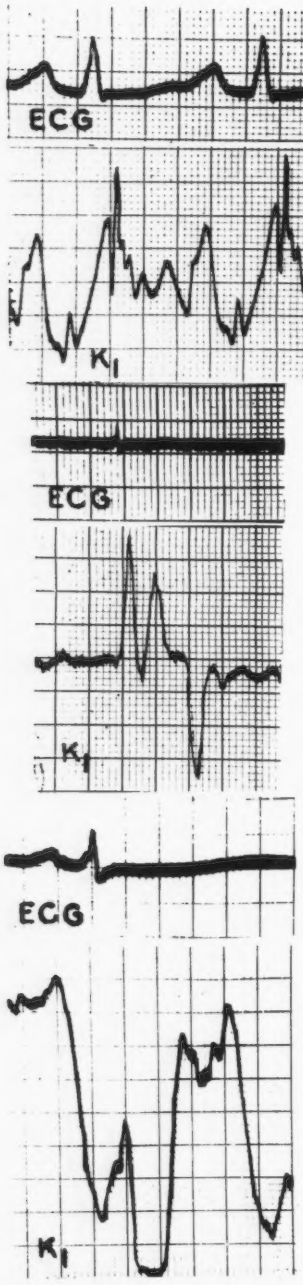

FIG. 4 *Top.* Mitral stenosis. Paper speed 50 mm. per second. Note (1) the small upstroke starting .03 second after the onset of P, which is superimposed on the preceding more abrupt upstroke; (2) the large biphasic downstroke that starts .06 second after P and that is ascribed mainly to contraction of the left atrium; (3) the terminal portion of this downstroke, which is thought to be related to relaxation of the right atrium; (4) the large terminal upstroke beginning .01 second before the QRS, which is believed to represent relaxation of the left atrium and which is apparently augmented by ventricular forces. The cause of the small up-down motion beginning .05 second before the QRS is uncertain. *Middle.* Mitral stenosis—atrial fibrillation. Paper speed 25 mm. per second. Note that the first large deflection is abrupt and starts .04 second after the onset of the QRS. The usual large atrial forces are absent. *Bottom.* After conversion to sinus rhythm. Paper speed 50 mm. per second. Same subject as *Middle.* Following conversion to normal rhythm, the atrial forces have appeared. These consist of a small initial upstroke and a huge downstroke after the onset of the P wave and before the beginning of the QRS. Note similarity of these forces to those in *Top.*

3. *Second Forward Motion.* This movement was present at all areas in most normal subjects. The onset was .16 ± .02 second after the beginning of the P wave in the K_1 region, but was more variable in the regions to the left of the sternum. In normal subjects, the beginning of this upstroke is frequently .01 to .02 second after the beginning of the QRS. Nevertheless, the movement is apparently not of ventricular origin because it frequently starts before the QRS, and, likewise, because it was present following isolated P waves in each of 3 patients with heart block (fig. 2). This movement began later (.23 ± .03 second) after the beginning of the P wave in such patients than in normal subjects. The reasons for this are unknown.

This second upstroke appeared to be somewhat larger in patients with mitral stenosis than in normal subjects, but definite conclusions concerning amplitude of this motion cannot be drawn because it is usually interrupted by ventricular forces shortly after it begins.

B. *Lateral Movements*

A typical lateral ballistocardiogram is illustrated in figure 5. The normal lateral motions of the body and of the axillary interspaces in relation to atrial contraction are summarized in table 2. The ballistocardiogram typically displayed a rightward-left-

ard-rightward sequence starting after the nset of atrial and before the onset of entricular excitation. The axillary kineto-ardiograms were complex, displaying at east 5 and often 6 directional changes be-ween the P and Q waves of the electrocardio-gram. The factors possibly responsible for hese movements are considered later.

Discussion

In the study of atrial movements, it would appear that records obtained from the right parasternal (K_1) region are likely to be the most useful. The findings in this area in normal subjects, and in the individuals with mitral stenosis, were more constant than the movements encountered to the left of the sternum. Consequently, the discussion will be centered mainly on the motions in this area.

The observations that have been mentioned indicate that the main anteroposterior movements occurring in relation to atrial activity are 3: namely, forward, backward, and then forward. Although these movements are small in relation to the subsequent ventricular motions, they are clearly related to atrial forces and not artifacts. Thus they are present in patients with heart block following isolated P waves (fig. 2), and are absent in subjects with atrial fibrillation (fig. 4*B*).

The *initial forward movement* is probably related to contraction of the right atrium. This chamber is excited first, and vector studies indicate that the excitation wave spreads leftward, forward, and footward.[3] The forward movement begins about .05 second after he onset of the P wave, which corresponds to he beginning of the right atrial pressure ise found by Testoni et al.[4] The movement s often largest in the region of the right atrium, and is inconstant in other areas. Unlike he following initial backward movement, his forward motion is not consistently increased in patients with mitral stenosis. In of 7 patients with cor pulmonale, this motion was greater than in any normal subject, nd in the remaining 2 patients it was greater han the average for normal persons.

This forward movement consequent to right trial contraction is usually greater in the

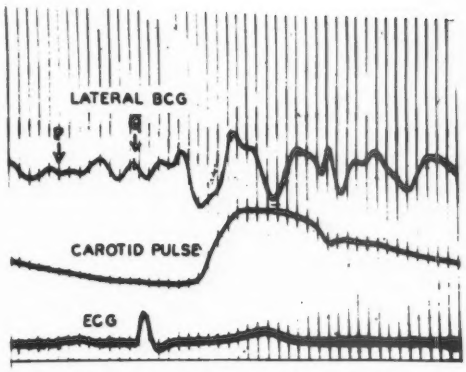

Fig. 5. The lateral ballistocardiogram of a normal subject is illustrated. The time lines indicate intervals of .02 second. An upstroke indicates rightward motion. There are 3 movements in the ballistocardiogram occurring between P and Q in the electrocardiogram. At .04 second after P there is a rightward movement followed by a leftward movement at .08 second. The second rightward movement occurs at 0.11 second after P. The relative importance of atrial and ventricular forces in the production of the second leftward motion is uncertain.

right than in the left parasternal area. It therefore does not seem to be due entirely to filling of the right ventricle. It does not appear to represent a venous A wave in the superior and inferior cavae, because the movement is not greater in the first and second (superior caval region) and fifth and sixth interspaces (inferior caval area) than in the third and fourth interspaces. It therefore seems likely that this upstroke, which is consistently present in all interspaces in the right parasternal region, represents a rightward pull on the heart by the right atrium. This chamber is fixed by the 2 cavae and shortening of its fibers would be expected to pull the remaining portions of the heart rightward, even though the right border moves leftward, as has been demonstrated by electrokymographic studies.[5, 6]

A rightward pull by the right atrium might tend to produce an inward motion in the left parasternal region. On the other hand, the filling of the right ventricle consequent to right atrial contraction would be expected to produce an outward movement in this area. Thus the inconstancy of the

movements in the left parasternal region at this time could be accounted for by a varying balance between two opposite forces.

The lateral ballistocardiogram exhibited a rightward-leftward sequence as the precordium moved forward (fig. 5). This can be ascribed to recoil followed by impact as blood moves from the right atrium to the right ventricle.

The axillary interspaces usually displayed rightward motion, starting slightly before the forward movement (table 2). This is in keeping with the concept that the initial effect of right atrial contraction is to pull the heart to the right. The succeeding leftward movement that occurred in traces from both axillae may conceivably have been due either to right ventricular filling or to sudden displacement of the interatrial septum to the left by the rising pressure in the right atrium.

The *backward motion*, starting about .10 second after the onset of the P wave, is nearly always greater in the right parasternal region in patients with mitral stenosis than in normal subjects. It is often increased in persons with mitral insufficiency, and in subjects with coronary disease or hypertension. The time of onset of this motion corresponds well with the inward movement of left atrial contraction, as seen in electrokymograms (Dussaillant[7]), and was slightly later than the rise in left atrial pressure (Braunwald et al.[8]). These observations would suggest that this backward motion is related to contraction of the left atrium. Since this chamber is fixed posteriorly by the pulmonary veins, its contraction would be expected to exert a backward and leftward pull on the heart.

The axillary interspaces displayed 2 motions that may be related to contraction of the left atrium. The first of these was leftward, at .09 ± .02 second after the P onset, and can probably be attributed to a leftward pull on the heart. The second and larger deflection, occurring about .03 second later, was rightward and was associated with a rightward motion in the ballistocardiogram (fig. 5, table 2). Relaxation of the right atrium probably begins at about this time and might be associated with rightward recoil as the liver begins to empty, or with a rightward impact as the interatrial septum suddenly is shifted to the right by the rising and falling pressures in the left and right atria, respectively.

The *terminal forward movement*, starting about .16 second after the onset of P, offers some difficulty in interpretation because it is soon interrupted by forces that are clearly of ventricular origin. This is indicated by their abrupt nature, their large magnitude, and their onset about .03 to .04 second after the beginning of the ventricular complex of the electrocardiogram. Such ventricular forces make it impossible to study the amplitude of this terminal forward movement. Possibly it is related to left atrial relaxation, because its direction is opposite to that of the force associated with left atrial contraction, and it appears to be exaggerated in some patients with mitral stenosis.

This division of the atrial forces into 3 phases represents an oversimplification. The axillary kinetocardiograms of normal subjects usually showed 6 motions, and certain patients with cardiac disease display evidence of more than 3 anteroposterior movements. The backward motion may be diphasic (figs. 2 and 4*A*), and probably is related not only to contraction of the left atrium, but also to relaxation of the right. However, the 3 forward-backward movements that have been described are constant in normal subjects, and afford a point of departure for the study of atrial movements in patients with cardiac disorders.

We have been surprised at the failure to find patients with mitral stenosis, regular rhythm, and evidence of diminished force of left atrial contraction. This would be expected if there is a descending limb of the atrial Starling curve. Possibly, the atrium responds to overdistention, with fibrillation rather than with diminished strength of coordinated contractions. More detailed studies of a large number of subjects are needed to settle this point.

In regard to any possible diagnostic significance of precordial atrial motions, the fol-

TABLE 2.—*Lateral Movements of Ten Normal Subjects in Relation to Atrial Contraction*

Time after onset of P, (seconds)		.03 ± .01	.05 ± .03	.07 ± .02	.09 ± .02	.12 ± .02	.15 ± .02
xillary KCG	Direction of motion	Rightward	Leftward	Inconstant and small rightward in 6 subjects	Leftward	Rightward	Leftward
	Number of subjects showing motion	7	9		8	10	7
	Range of relative amplitude	1/20 to 1/4	1/25 to 1/5		1/25 to 1/4	1/9 to 1/2	Interrupted by ventricular forces
Lateral BCG	Direction of motion	----	Rightward	Leftward	Previous leftward motion continues	Rightward	Previous rightward motion continues
	Number of subjects showing motion	----	8	8		8	
Possible cause of motions		Rightward pull by right atrium (KCG)	Right ventricular filling (KCG): recoil as rt. atrium ejects (BCG)	Impact of blood on rt. ventricle (BCG)	Leftward pull by left atrium (KCG)	Relaxation of rt. atrium with move of interatrial septum to rt. (KCG) & rightward recoil as liver empties (BCG)	Leftward movement of interatrial septum as left atrium relaxes (KCG)

lowing may be stated: The presence of marked exaggeration of the left atrial backward motion does not per se constitute significant evidence for mitral stenosis, because such exaggeration is not invariably present. Likewise, it is frequently seen in patients with mitral insufficiency, and in subjects with other types of cardiac disease. The absence of this phenomenon in a patient with sinus rhythm would appear to constitute some, but not conclusive, evidence against a dynamically significant degree of mitral stenosis. The same reasoning appears to apply, although less emphatically, to the relationship between cor pulmonale and augmentation of the initial forward motion of right atrial contraction. Thus it would appear that the precordial motions occurring between the P and Q waves of the ballistocardiogram may be of some value in differentiating mitral stenosis from cor pulmonale but are at present of limited if any value in distinguishing these two conditions from other causes of left and right heart stress, respectively.

Patients with congenital cardiac disorders have been omitted from this study because their atrial and other precordial motions are often so bizarre as to defy interpretation at the present time. In patients with acquired heart disease who have no evidence of valvular lesions, it would appear that exaggeration of one or both of the deflections ascribed to atrial contraction may indicate either (1) an absolute increase in atrial force, probably caused by incomplete ventricular emptying, with some increase in residual atrial blood, or (2) an absolute decline in magnitude of ventricular precordial motion, with only a relative increase in atrial force, or (3) a combination of these two situations. In any event, the occurrence in such a subject of increase in the relative magnitude of the precordial motions induced by atrial contraction is perhaps suggestive of decrease in the reserve power of the corresponding ventricle. Because of the great variation in normal subjects of the relative magnitude of these atrial motions, it would seem

advisable to study a series of individuals during various degrees of cardiac failure before arriving at definitive conclusions concerning this point. Such studies are in progress and will be the subject of a later report.

Summary

Precordial motions beginning between the onset of the P and Q waves of the electrocardiogram have been studied in a group of normal subjects, and in patients with various types of cardiac disease. During this portion of the cardiac cycle tracings from the right parasternal region have appeared to yield more consistent findings than records taken to the left of the sternum. A sequence of motions consisting of forward-backward-forward was regularly observed. These motions are clearly of atrial origin because they were absent in patients with atrial fibrillation, and were observed following isolated P waves in each of 3 subjects with heart block.

About .05 second after the onset of the P wave, a small rightward and forward motion occurred. This motion did not exceed one fourth of the total amplitude of the cardiac cycle in any of the normal subjects. It was greater than the average normal amplitude in each of 7 subjects with cor pulmonale, and in 5 of these was outside the normal range.

About .10 second after the onset of the P wave a backward and leftward motion occurred. This was exaggerated beyond the normal range in most of the 30 traces from patients with mitral stenosis, and in 7 of 10 records from subjects with "pure" mitral insufficiency. This movement is mainly ascribed to contraction of the left atrium, which being fixed posteriorly by the pulmonary veins appears to pull the heart backward. Since the motion is sometimes biphasic, it is probable that relaxation of the right atrium may also be a contributing factor.

Patients with various types of myocardial disease may or may not show exaggeration of either or both these movements. It therefore appears that exaggeration of these atrial motions may be related to (1) a direct strain on the corresponding atrium due to a valve lesion; (2) an indirect strain due to disease or overload of the corresponding ventricle.

Aside from these 2 movements that are ascribed to successive contraction of the 2 atria, the traces exhibit a second upstroke, starting just before or after the onset of the QRS of the electrocardiogram. This motion is tentatively ascribed to relaxation of the left atrium, but it cannot be studied in detail because it is soon interrupted by the larger motions due to ventricular contraction.

Lateral ballistocardiograms (low-frequency acceleration) appear to reflect right atrial activity. They exhibit a rightward-leftward-rightward sequence ascribed respectively to recoil, impact and, possibly, to right atrial relaxation.

The motions of the axillary interspaces, as recorded by the kinetocardiographic technic, are complex and usually exhibit 6 directional changes between the onset of P and the beginning of ventricular contraction. Possible causes of these movements have been considered.

The study of the precordial reflections of atrial motion would appear to have only very limited diagnostic value. Such motions may possibly be of aid in deciding whether mitral stenosis is dynamically significant, and in differentiating between mitral stenosis and cor pulmonale. At present, they are of little or no aid in distinguishing mitral stenosis from insufficiency, or from left ventricular failure.

Summario in Interlingua

Le movimentos precordial que se initia inter le declaration del unda P e le declaration del unda Q in le electrocardiogramma esseva studiate in un gruppo de subjectos normal e in patientes con varie typos de morbo cardiac. Durante le mentionate portion del cyclo cardiac, registrationes ab le dextere region parasternal pareva resultar in constatationes plus regular que registrationes ab le region al sinistra del sterno. Un sequentia de movimentos consistente de proverso-retroverso-proverso esseva observate regularmente. Iste movimentos es clarmente de origine atrial, proque illos esseva absente

in patientes con fibrillation atrial e esseva observate post isolate undas P in cata un de tres subjectos con bloco cardiac.

Circa 0,05 secundas post le declaration del unda P, un miere movimento dextroverse e proverse se manifestava. Iste movimento non excedeva un quarto del amplitude total del cyclo cardiac in ulle del subjectos normal. Illo esseva plus grande que le normal amplitude medie in cata un de 7 subjectos con corde pulmonal, e in 5 de istes illo esseva foras del limites normal.

Circa 0,10 secundas post le declaration del unda P, un movimento retroverse e sinistroverse se manifestava. Isto esseva exaggerate in ultra del limites normal in le majoritate del 30 registrationes ab patientes con stenosis mitral e in 7 inter 10 registrationes ab subjectos con "pur" insufficientia mitral. Iste movimento es ascribite principalmente a contraction del atrio sinistre. Proque le atrio es fixate posteriormente per le venas pulmonar illo pare traher le corde in retro. Viste que le movimento es a vices biphasic, il es probabile que relaxation del atrio dextere es etiam un factor contributori.

Patientes con varie typos de morbo myocardial exhibi o non exhibi exaggerationes del un o del altere o de ambes de iste movimentos. Ergo il pare que le exaggeration de iste movimentos atrial es relationate (1) a un effortio directe in le atrio correspondente, causate per un lesion valvular, (2) a un effortio indirecte causate per morbo o excesso de carga in le ventriculo correspondente.

A parte iste 2 movimentos que es ascribite al contraction successive del 2 atrios, le registrationes exhibi un secunde tiro in alto, comenciante justo ante o post le declaration de QRS. Iste movimento es ascribite tentativemente a relaxation del atrio sinistre, sed illo non pote esser studiate in detalio proque illo es tosto interrumpite per le plus marcate movimentos que es causate per le contraction ventricular.

BCG's lateral (acceleration a basse frequentia) pare reflecter activitate dexteroatrial. Illos exhibi un sequentia dexteroverse-sinistroverse-dexteroverse, ascribite—respectivemente—a reculamento, impacto, e—possibilemente—relaxation dextero-atrial.

Le movimentos del interspatios axillar, registrate per le technica cinetocardiographic, es complexe e exhibi usualmente 6 alterationes directional inter le declaration de P e le comenciamento del contraction ventricular. Causas possibile de iste movimentos es discutite.

Il pare que le studio del reflexiones precordial de movimente atrial possede solmente un limitate valor diagnostic. Il es possibile que iste movimentos se prova utile in determinar si stenosis mitral es dynamicamente significative e in differentiar inter stenosis mitral e corde pulmonal. Al tempore presente, illos es de pauc o nulle adjuta in distinguer stenosis mitral ab insufficienta o stenosis mitral ab disfallimento ventricular.

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Comparative Severity of Atherosclerosis in Costa Rica, Guatemala, and New Orleans

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The present study is concerned with the comparative severity of aortic atherosclerosis in specimens obtained from 941 necropsies performed in low-income Costa Ricans, Guatemalans, and New Orleans whites. The findings indicate geographic differences in the severity of atherosclerosis after the age of 30 years. The dietary habits, serum cholesterol, and lipoprotein patterns of similar populations are compared with the present pathologic findings.

PREVIOUS studies have described the relative extent and severity of atherosclerosis observed in aortas taken from unselected autopsies of a group of low-income Guatemalans as compared to a similar group of United States inhabitants in New Orleans.[1, 2] These reports indicated that the early lesions of aortic atherosclerosis, which simple fatty streaks are presumed to represent, developed at very nearly the same rate in both groups up through the third decade; but the more advanced changes—fibrous plaques, ulceration, hemorrhage, thrombosis, and calcification—were much less severe in the Guatemalans than in the individuals from New Orleans. These population samples represented individuals dying in a large general charity hospital in each area, and consequently represented the lowest income groups of both regions. Racially, however, the 2 groups were quite distinct. The United States white population as a whole is characterized by an approximate 45 per cent incidence of blood group "O."[3] On the other hand, the low-income Guatemalans of pure or predominant Mayan Indian extraction as noted by their physical appearance and way of life, have a blood group "O" frequency ranging from 80 to 96 per cent depending on the village studied.[4, 5] Since the racial differences between the 2 regional groups were as prominent as the differences in dietary habits and serum lipoprotein and cholesterol values,[6] the relationship of the latter factors to the atherosclerotic lesions could not be evaluated. A solution to this problem was sought by studying in a similar manner the prevalence of atherosclerotic lesions in individuals from Costa Rica. The low-income Costa Rican population is predominantly white[4] as indicated by history, appearance, and blood-group distribution, but their living conditions are similar to those for comparable socioeconomic groups in Guatemala. Moreover, data on their dietary habits and on their serum cholesterol and lipoprotein concentrations are available[6, 7] for comparison with the extent and severity of atherosclerotic lesions.

It should be pointed out and emphasized here that these studies are based on visual assessment of the actual atherosclerotic lesions in the aorta, in contrast with many other studies in which the incidence of various clinical manifestations of arterial disease has been determined.[8–13]

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Materials and Methods

Three hundred and ninety-eight aortas were obtained from unselected autopsies at the San Juan de Dios Hospital, San José, Costa Rica, a large charity institution. The number of cases in

TABLE 1.—*Number of Cases by Age Group*

Age in years	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	Over 80	Total
New Orleans whites	42	25	33	28	20	27	26	16	12	229
Guatemala	31	20	39	62	50	47	34	22	9	314
Costa Rica	131	24	27	34	42	56	45	31	8	398

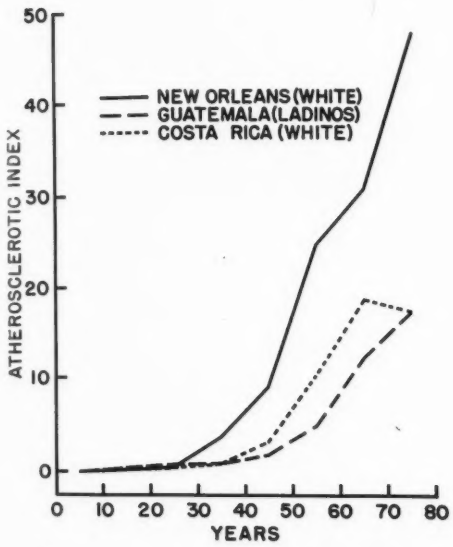

FIG. 1. Severity of aortic atherosclerosis.

each decade is listed in table 1, together with a similar tabulation of the New Orleans and Guatemala cases.

Prior to examination the aortas, which had been fixed in 10 per cent formalin, were stained with Sudan IV. Examination was completed with no knowledge of age, sex, race, cause of death, or associated disease processes. The extent and severity of atherosclerosis was evaluated according to the procedure previously described.[14] This method takes into consideration both the type of lesion and the relative surface extent of each. Intimal lesions are classified in 4 grades: grade I, fatty streaks; grade II, fibrous atheromatous plaques; grade III, necrotic, ulcerated, hemorrhagic or thrombotic plaques; grade IV, calcified plaques.

In terms of area, surface involvement is estimated and recorded in 1 of 5 groups as follows: group O, less than 5 per cent surface involvement; group A, 6 to 15 per cent surface involvement; group B, 16 to 33 per cent surface involvement; group C, 34 to 50 per cent surface involvement; group D, more than 51 per cent surface involvement.

The findings are incorporated into an "atherosclerotic profile," a 5-digit figure that expresses both the proportion of the intima that is diseased and the decimal fraction of the diseased portion made up by each of the 4 types of lesions. By appropriate weighting, the elements of the profile are integrated and an index of atherosclerosis is derived that expresses severity on a scale ranging from 0 to 100.

RESULTS

As reflected by the atherosclerotic index, the progression of the severity of atherosclerosis with age is depicted in figure 1. Significant differences in the weighted index of atherosclerosis in the 3 countries were not observed before the age of 30. Subsequently, intimal disease appeared to develop more rapidly in New Orleans than in either Guatemala or Costa Rica. After the age of 40, but not before, atherosclerosis increases more rapidly in Costa Rica than in Guatemala, although it is still significantly less than in New Orleans.

When the data were analyzed only for the *extent* of intimal surface involvement (fig. 2) geographic differences still did not appear before the age of 30 years. In all 3 localities, virtually all aortas showed some degree of intimal disease by the end of the first decade. After age 30, the extent of involvement increased progressively with age; most rapidly in New Orleans, least rapidly in Guatemala. At the age of 50, for example, the proportion of aortas with more than half the intima diseased was 54 per cent in New Orleans, 47 per cent in Costa Rica, and 28 per cent in 100 per cent of the New Orleans aortas showed over half of the surface involved; the Guatemala. At both 70 and 80 years of age, corresponding figures were 85 and 92 per

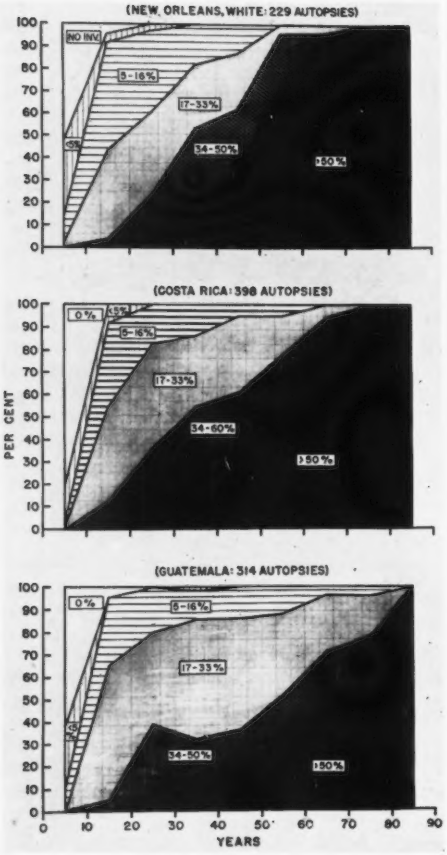

FIG. 2. Amount of aortic surface involvement with atherosclerosis.

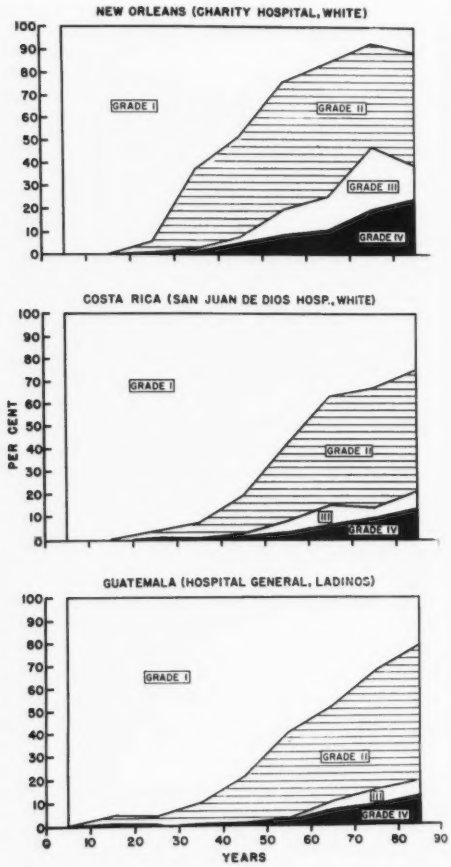

FIG. 3. Aortic type of atherosclerotic involvement.

cent in Costa Rica and 54 and 78 per cent in Guatemala.

Again, with increasing age, *the relative proportions of the 4 grades of atherosclerotic lesions* shifted toward an increase in the more advanced types (fig. 3). During the first 2 decades, lipid streaks (grade I) predominated; less than 5 per cent were fibrous plaques (grade II); and there were no complicated (grade III) or calcified lesions (grade IV). During the third decade, fibrous plaques (grade II) became more numerous, especially in the New Orleans material. Prior to 30 years of age there were only infrequent lesions that were complicated or calcified. Beginning with the fourth decade, there was a progressive increase in the proportion of grade III or IV lesions. The rate of increase was greatest in New Orleans, intermediate in Costa Rica, and least in Guatemala. For instance, in the sixth decade, 20 per cent of the lesions in New Orleans were grade III or IV in type, while the corresponding figures for Costa Rica and Guatemala were 8 and 3 per cent respectively. By the eighth decade, the same lesions comprised 48, 15, and 15 per cent of the aortic disease in the 3 respective localities.

DISCUSSION

As a result of this comparative study, it appears that up to 30 years of age the development of atherosclerotic lesions is similar

in quality and degree in the population samples examined from New Orleans, Costa Rica, and Guatemala. These conclusions are supported by the assessment of lesions in the same material by 2 different pairs of individuals using methods similar in principle.[2]

However, this particular study has shown that after 30 years of age there are differences in the severity of the process in the 3 groups. The highest rate of development is apparent in New Orleans as indicated by both a greater surface extent of the disease and a higher proportion of advanced lesions. Severe lesions appear less rapidly in Costa Rica and more slowly still in Guatemala. The previous study[2] also showed the fibrous plaques in New Orleans aortas to be much more extensive than in the aortas from either of the 2 Central American countries by the age of 40 years.

Since Costa Ricans and New Orleans whites are both principally of European extraction, racial factors are unlikely to be primarily responsible. Therefore, environmental factors must be sought to account for these differences.

Of possible environmental factors, diet appears at present to be one of the most important. Differences in serum cholesterol and lipoprotein concentration have been reported[6, 7] and related to the dietary habits prevalent in the United States, Guatemala, and Costa Rica. It is interesting to note that, virtually paralleling the difference in atherosclerosis reported above, the caloric and fat intakes are the highest in the United States, considerably less in rural Costa Rica, and still lower in rural Guatemala. In fact, more than per cent of the total calories in the United States diet are derived from fat, compared to per cent in Costa Rica, and 7.5 per cent Guatemala.[6, 7] Dietary fat and protein of animal origin are high in the United States, low in rural Costa Rica, and still lower in rural Guatemala. In like fashion, serum cholesterol levels are relatively high in the United States, low in rural Costa Rica, and still lower in rural Guatemala.[6] The relatively low serum cholesterol levels and severity of atherosclerosis were not associated with lower S_f 12 and higher lipoprotein fractions[6, 7] than in the United States population. S_f 12-20 and S_f 20-100 levels were even lower in Costa Rican males than in comparable Guatemalan and United States samples, and Costa Rican females had higher values than females of the other 2 groups. Further examinations showed, however, that the S_f 0-12 levels were low in Costa Rica by an amount sufficient to account for the lowered cholesterol levels. Certainly, in this population serum levels of the S_f 12-20 and S_f 20-100 lipoprotein fraction did not parallel the severity of atherosclerosis, while S_f 0-12 levels and serum cholesterol both appeared to do so.

In connection with the mechanism by which the etiologic agent, whatever that may be, produces the atherosclerotic lesions, it is of interest to note that the differences found are in the advanced lesions and are not in the simple intimal lipid deposits encountered during the first 3 or 4 decades of life. If the relationship between serum lipids and atherosclerotic lesions demonstrated here is actually a causative relationship and not a coincidental one, the data suggest that the mechanism is not one of perfusion and filtration of the arterial wall with lipid-rich plasma, but has something to do with the inflammatory and reparative reaction in and around the atheromatous plaques.

It is possible that the chemical type of lipid deposited in the early fatty streak is different in the aortas from each area, so that one combination of lipid is more injurious and excites a more intense reaction than another. Since the method of evaluation used here does not take into account the concentration of lipid material in the tissue, it is also possible that the amount of lipid per unit of tissue differs. Qualitatively different lipids may furthermore influence the coagulative mechanism in either direction, leading to an increased tendency to hemorrhage within the plaque or thrombosis on its surface. These possible interpretations have been discussed extensively in previous reports.[2]

Attractive though the assumption of a causal relationship between diet, serum lipids,

and atherosclerosis may be, certain gaps in the chain of evidence and criticisms of the presently reported data must be pointed out. For one, the dietary habits of the population group represented by the New Orleans sample have not been as specifically determined as those for the Guatemalan or Costa Rican groups. This part of the United States cannot be accepted as "average" for the United States population, as it is culturally and geographically rather unique. Furthermore, although we believe that the people dying in large general charity hospitals offer the most reproducible autopsy population sample available, the possibility of biased selection remains. The size of the sample for each group is being continually increased, so that it should soon be possible to make not only age-specific but also sex-specific and cause of death-specific comparisons. Finally, it must be remembered that these data deal only with aortic lesions, and that a correlation of aortic with coronary and cerebral lesions remains to be firmly established.

Summary

The incidence and severity of aortic atherosclerosis was studied in 941 aortas obtained from autopsies performed on low-income Costa Ricans, Guatemalans, and New Orleans whites. The study covered cases ranging from 1 to 80 years of age and the findings indicated geographic differences in the severity of aortic atherosclerosis after the age of 30 years. The severity of involvement with atherosclerotic lesion as indicated by 3 different indices was greatest in New Orleans, intermediate in Costa Rica, and lowest in Guatemala. The dietary habits, serum cholesterol, and lipoproteins previously reported in the 3 countries were compared with the pathologic findings. There is an apparent correspondence between the dietary fat intake, the serum cholesterol levels, S_f 0-12 lipoprotein patterns, and the degree of aortic atherosclerotic lesions as measured by these methods.

Summario in Interlingua

Le incidentia e le severitate de atherosclerosis aortic esseva studiate in 941 aortas obtenite ab necropsias de individuos a basse stato economic de Costa Rica, Guatemala, e le population de racia blanc in Nove Orleans. Le studio includeva casos con etates de inter I e 80 annos. Le resultatos indicava le existentia de differentias geographic in le severitate de atherosclerosis aortic post le etate de 30 annos. Le severitate del lesiones atherosclerotic – evalutate super le base de 3 differente indices —esseva le plus marcate in Nove Orleans, intermediari in Costa Rica, e le minus marcate in Guatemala. Le habitudes dietari, le valores pro cholesterol seral, e le valores pro lipoproteinas reportate previemente in le 3 areas esseva comparate con le constatationes pathologic. Le methodos usate resultava in le conclusion que il existe un correspondentia apparente inter le ingestion dietari de grassia, le nivellos seral de cholesterol, le configuration del lipoproteinas de S_f 0-12, e le gradо del lesiones de atherosclerosis aortic.

Acknowledgment

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MacDonald, A., and Robbins, S. L.: The Significance of Nonbacterial Thrombotic Endocarditis: An Autopsy and Clinical Study of 78 Cases. Ann. Int. Med. **46**: 255 (Feb.), 1957.

Seventy-eight cases of nonbacterial thrombotic endocarditis occurring over the past 22 years among 18,486 consecutive autopsies at the Mallory Institute of Pathology at the Boston City Hospital were analyzed. From a clinical standpoint, the patients were separated into 3 groups. The first group in which embolization of organs constituted the chief clinical picture may permit of antemortem diagnosis. In a patient with cardiac decompensation and evidence of embolization of several organs, the important differentiation is between nonbacterial thrombotic endocarditis, bacterial endocarditis, and mural thrombi of the cardiac chambers. In the second group, in which embolization is at least partially masked by a more primary disease, diagnosis is more difficult and may be considered when a patient in the elderly age group confined to bed develops symptoms consistent with embolization of organs which do not constitute a phase of the natural history of the primary disease. Diagnosis in the third group in which there is no embolization of organs and in which the valvular lesions constitute an incidental finding at autopsy is probably not possible. In 11 cases, emboli were found that were considered to have arisen from the valvular vegetations and to have caused or contributed to the patient's death. The organs principally involved were the brain, the spleen, and the kidneys. The most commonly associated diseases in this series were cancer (36 per cent), heart failure (30 per cent), and vascular thromboses (27 per cent). The pathogenesis of the vegetations is considered to be the occurrence of thrombi formed from blood within the cardiac chambers upon nonspecific areas of focal fibrocollagenous degeneration of valves. When embolization occurs, it is considered to be the result of a portion of adherent thrombus breaking off into the circulation. The main feature pathologically is the lack of cellular reaction in the involved valve in nonbacterial thrombotic endocarditis in contrast to the other types such as acute bacterial endocarditis, subacute bacterial endocarditis, healed bacterial endocarditis, healed rheumatic endocarditis, active rheumatic endocarditis, and the atypical verrucous endocarditis of Libman-Sacks.

WENDKOS

Effect of Potassium on Conduction and Ectopic Rhythms in Atrial Fibrillation Treated with Digitalis

By Charles Fisch, M.D., J. Paul Shields, M.D., S. Anthony Ridolfo, M.D., and Harvey Feigenbaum

Intravenous administration of potassium to patients with atrial fibrillation treated with digitalis resulted in depression of conduction through the A-V node, appearance of complete A-V dissociation and in some abolition of ventricular ectopic beats. The presence or absence of ectopic ventricular beats as well as the degree of depression of A-V node could be controlled at will by varying the rate of infusion. Termination of infusion was paralleled by prompt reappearance of all arrhythmias present before infusion started.

POTASSIUM is used in the treatment of cardiac arrhythmias due to digitalis as well as some arrhythmias not associated with digitalis therapy.[1-10] A number of the latter no doubt represent cases of arrhythmias secondary to potassium depletion such as are encountered in diarrheal states, vomiting, and severe heart failure.[11, 12] There are instances of cardiac arrhythmia, however, in which potassium depletion cannot be demonstrated, nor is there reason to suspect that a state of depletion exists; yet some of these respond to potassium.[13] It is very likely that the response of many of these arrhythmias is due to the well-known, nonspecific, depressing effect of potassium and may have nothing whatever to do with replacement of serum or total body potassium or "antagonism" to digitalis. The direct relation of the degree of depression of myocardium to the rate of infusion and the concentration of potassium delivered to the heart itself was stressed in 1930 by Wiggers.[14] Elevation of serum potassium has been noted to decrease conduction through the A-V node. Such a depression of conduction is manifest by prolongation of P-R intervals and occasionally by A-V dissociation due to interference. In patients with atrial fibrillation the depression of conduction is manifest by slowing of ventricular rate. Higher grades of block such as second degree or complete A-V dissociation have not been observed in humans.[15, 16]

Because of these earlier reports it was thought that this problem warranted further study with emphasis on (1) the relation of changes of ventricular rate and rhythm to rate of infusion and (2) the speed with which such changes may take place. Patients with atrial fibrillation seemed best suited for such an investigation because (1) it is easier to determine the "degree" of digitalization in patients with atrial fibrillation than in individuals with sinus rhythm; (2) if potassium and digitalis have an opposite effect, then administration of potassium to individuals with atrial fibrillation and A-V nodal escape beats or A-V nodal escape rhythm due to digitalis should result in increased A-V conduction with speeding of ventricular rate and disappearance of A-V nodal escape beats and A-V nodal rhythms; and (3) if disappearance of ectopic ventricular beats were due to opposite effects of potassium and digitalis, it should be accompanied by simultaneous increase in A-V conduction and speeding of ventricular rate.

Method

Seventeen patients with atrial fibrillation with varying forms of heart disease were selected from the Robert Moore Heart Clinic and wards of Indianapolis General Hospital. All but one had su-

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TABLE 1.—*Effect of Potassium on Heart Rate and Rhythm*

tient	Solution infused	Rate of infusion	Ventricular rate prior to infusion of potassium	Slowest ventricular rate during infusion of potassium	Change in rhythm	Ventricular rate 2 hours after infusion	Serum potassium levels (mEq. per L.)			
							Before infusion	During infusion	End of infusion	1 hour after infusion	2 hours after infusion
1	K phosphate	Varying	50	34	A-V dissociation	60	4.9	6.2	6.7		5.5
2	K phosphate	Varying	53	35	A-V dissociation	57	5.7	4.7	5.3	5.9	5.7
3	NaCl-KCl	Varying	60	41	A-V dissociation	69	5.4	4.6	4.8		4.4
4	K phosphate	Varying	63	39	A-V dissociation and disappearance of ventricular bigeminy	65	5.5	4.0, 4.7	5.9		4.9
5	K phosphate	Varying	57	40	Appearance of ventricular escape beats and idioventricular rhythm	76	5.3	4.0	4.7		6.3
6	K phosphate	Varying	68	45	Disappearance of ventricular escape Beats and idioventricular rhythm	65	5.0	5.4	7.0		6.6
7	NaCl-KCl				A-V dissociation and disappearance of ventricular bigeminy		4.0	4.1	4.4	4.5	4.1
8	K phosphate	Varying	51	41	A-V dissociation	56	4.6	4.9	5.0		4.7
9	K phosphate	Varying	74	54	No change	89	5.7	4.5	5.1		4.9
10	K phosphate	Varying	74	65	A-V nodal escape beats	87	4.0				5.3
11	K phosphate	Varying	65	57	A-V nodal escape beats	73		4.7	5.3		4.6
2	K phosphate	Uniform	63	63	No change	79	4.6	4.7	5.5	5.6	5.0
3	NaCl-KCl	Uniform	60	60	No change	85	5.0	4.6	5.3	4.5	4.6
4	NaCl-KCl	Uniform	62	71	Speeding of A-V nodal rhythm present prior to infusion	68	3.3	2.7	3.6	3.9	3.5
5	NaCl-KCl	Uniform	89	79	No change	88	4.5	4.1	5.8		5.4
	NaCl-KCl	Uniform	88	58	A-V nodal escape beats	83	4.6	4.4	5.4	5.7	4.6
	NaCl-KCl	Uniform	78	78	No change	92	3.6				4.5

ventricular conduction, the latter (patient no. 1 had atrial fibrillation with complete A-V dissociation. Each patient was carefully examined and those falling in functional group IV or showing signs of renal impairment were excluded from the study. All patients were "fully" digitalized with digitoxin. The majority exhibited A-V nodal escape beats at the end-point of digitalization. So as not to be misled by the vagal effect of digitalis each patient was exercised and given 1.25 mg.

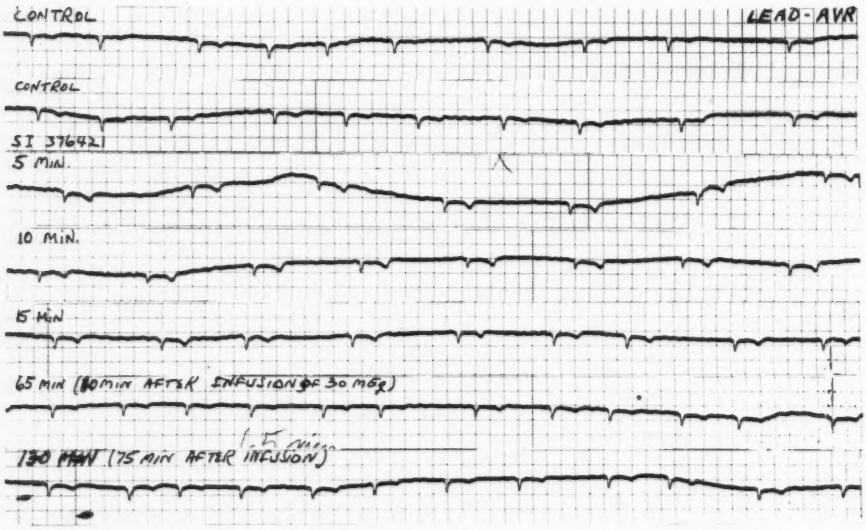

FIG. 1. This tracing shows atrial fibrillation with appearance of complete A-V dissociation. The rate of the A-V nodal pacemaker changes from 33 (*5-minute strip*) to 40 (*10-minute strip*) depending on the speed of infusion of potassium.

of atropine subcutaneously on the day prior to administration of potassium. Those who did not show a rise in ventricular rate over 90 were selected for further study.

Each patient rested for 30 minutes before administration of potassium was begun. Electrocardiograms were taken every 5 minutes during the control period and during infusion of potassium. Frequent tracings were taken thereafter for a period of 2 hours. Six patients (nos. 3, 6, 14–17) were given 200 ml. of isotonic saline over a 30-minute period before potassium was started. Eleven patients were given buffered potassium phosphate dissolved in distilled water to a concentration of 150 mEq. per liter and 6 other patients (nos. 3, 7, 14–17) received the potassium in form of potassium chloride. The rate of infusion was uniform in 6 patients and in 11 it was started at a rapid rate but this speed could not be maintained for longer than 3 to 5 minutes because of intense local pain. The average amount of potassium administered throughout the experiment varied from .5 to 1.0 mEq. per minute, depending on the degree of pain. The infusion was not discontinued until at least .5 mEq. per Kg. of body weight was administered. Six patients were given 1.25 mg. of atropine subcutaneously 2 hours after the administration of potassium was discontinued, and the ventricular rate was recorded for an hour. Serum potassium levels were determined during the control period, during the infusion, at the end of infusion, and 2 hours after the experiment was discontinued. The serum levels were determined by means of the Beckman flame photometer with a lithium interval standard.

The electrocardiograms were analyzed with regard to (1) ventricular rate, (2) presence or absence of ectopic ventricular complexes, (3) evidence of A-V nodal escape beats and A-V nodal rhythm, (4) change of T waves.

RESULTS

Effect on A-V Conduction and Ventricular Rate. Thirteen of the 17 patients exhibited a decided slowing of the ventricular rate during the infusion of potassium (table 1). In 6 individuals the ventricular slowing was secondary to a complete A-V dissociation (nos. 1–4, 7, 8). In 4 patients (nos. 5, 10, 11, 16) there were accompanying A-V nodal escape beats or A-V nodal rhythm and in 1 (no. 6) there was a disappearance of idioventricular rhythm. The patient (no. 14) with atrial fibrillation and A-V dissociation during the control period maintained the A-V dissociation throughout the experiment, but the ventricular rate did speed under the influence of the infused potassium.

In 2 of the patients (nos. 1 and 2) with complete A-V dissociation the rate of the

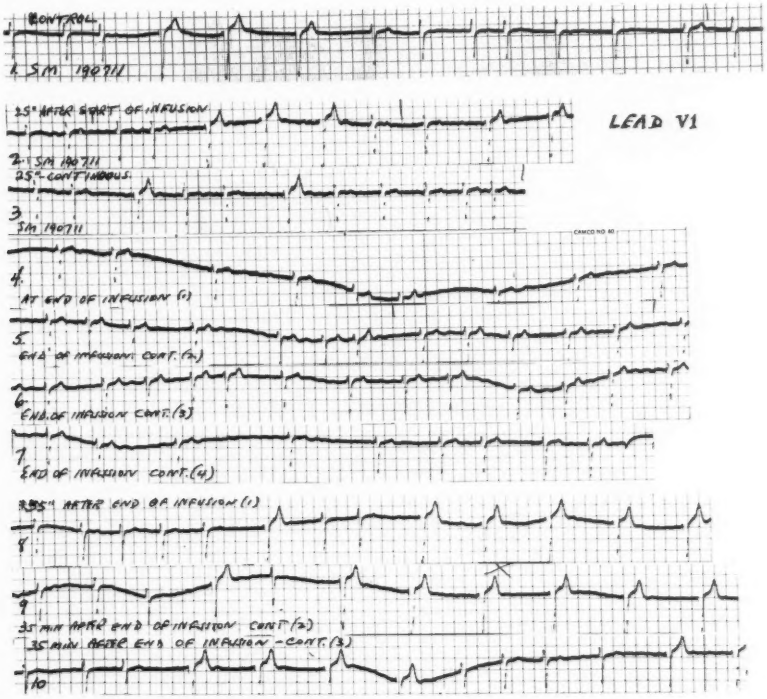
CONTROL
LEAD V1
END OF INFUSION (1)
END OF INFUSION CONT. (2)
END OF INFUSION CONT. (3)
END OF INFUSION CONT. (4)
35 MIN AFTER END OF INFUSION (1)
35 MIN AFTER END OF INFUSION CONT. (2)
35 MIN AFTER END OF INFUSION - CONT. (3)

FIG. 2. Atrial fibrillation with ventricular bigeminy showing appearance of A-V dissociation and disappearance of ventricular ectopic beats. These changes took place rapidly and were dependent entirely on rate of infusion of potassium.

pacemaker located in the A-V node (or bundle of His) varied with the speed of infusion of potassium. These changes are clearly demonstrated in figure 1 (patient 2). The control strip in this figure shows atrial fibrillation. Tracing taken 5 minutes after beginning of infusion of potassium and after 60 seconds of "wide-open" flow of the solution, shows complete A-V dissociation with R-R intervals of 1.80 seconds. At this point the patient experienced severe pain in the arm and the infusion was stopped. A tracing 5 minutes later still shows complete A-V dissociation but with a faster ventricular rate (R-R interval of 1.52 seconds). At this point a slower and more uniform rate of infusion of potassium was resumed. Fifteen minutes after start of the experiment supraventricular control of ventricles returned, interrupted by an occasional A-V nodal escape beat after an R-R interval of 1.50 seconds. The last 2 strips recorded 10 minutes and 75 minutes after the infusion of potassium was discontinued reveal atrial fibrillation with a ventricular rate similar to that noted prior to the experiment. A total of 30 mEq. of potassium was infused over a period of 55 minutes. The serum potassium levels were 5.7 mEq. before infusion, 4.7 mEq. midway in the infusion, 5.3 mEq. at the end of infusion, 5.9 mEq. 1 hour after infusion, and 5.7 mEq. 2 hours after infusion, respectively.

In 6 patients (nos. 1, 5, 9, 10, 12, 13) the ventricular rate 2 hours after the end of the administration of potassium exceeded the control rate by 10 beats per minute, the average rise being 16 beats per minute. In the remainder there was no rise or the increase was less than 10 beats per minute.

The 6 patients who received atropine 2

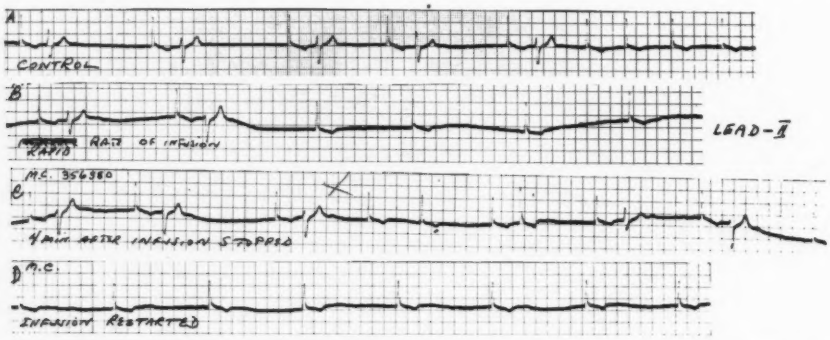

FIG. 3. Atrial fibrillation with ventricular escape beats and runs of idioventricular rhythm. The idioventricular rhythm was abolished and conduction via the A-V node depressed markedly during intravenous infusion of potassium. The ectopic beats reappeared after administration of potassium was stopped.

hours after infusion was discontinued exhibited ventricular speeding but the increase was not greater than that observed when atropine was administered on the day before administration of potassium.

Effect on Ventricular Ectopic Beats. During the administration of potassium the idioventricular rhythm (patient 6) and ventricular bigeminy (patients 4, 5, 7) disappeared either at the time of maximum depression of conduction through the A-V node (patients 5, 6) or with appearance of complete A-V dissociation (patients 4, 7). In all 4 patients in this group the ventricular ectopic beats reappeared: in 2 (patients 4, 5) within 5 minutes after the infusion was halted and in the other 2 (patients 6, 7) within 30 minutes after the infusion was discontinued. Elimination of the ventricular ectopic beats with simultaneous decrease or cessation of conduction through the A-V node and the effect of rate of infusion on such changes are shown in figures 2, 3,and 4.

In figure 2 (patient 6) *strip 1* shows atrial fibrillation with ventricular escape beats and idioventricular rhythm. A total of 30 mEq. of potassium was administered over a period of 54 minutes. The rate of injection varied but a rapid infusion was impossible because of severe local pain whenever an attempt was made to infuse the solution rapidly. *Strips 2 and 3* recorded 25 minutes after the experiment began, show no essential change except that the T waves were somewhat taller. At the end of infusion *(strips 4–7)* the T waves were upright and peaked. There was marked depression of A-V nodal conduction and long periods elapsed during which, on the basis of the control tracing, one would expect ventricular escape beats to appear. However, the ventricular escape beats did not occur, indicating depression of ectopic focus by potassium. Thirty-five minutes after infusion was stopped *(strips 8–10)* the T waves were much lower and rhythm seen in *strip 1* was again present.

In figure 3 (patient 4) the control tracing shows atrial fibrillation with a ventricular rate of 75 to 90 and a run of ventricular bigeminy. Serum potassium before infusion was 5.5 mEq. A total of 30 mEq. of potassium was infused over a period of 75 minutes. The infusion was begun at a rapid rate. Within 4 minutes *(strip B)* the ventricular bigeminy disappeared with simultaneous marked decrease of conduction through the A-V node. A serum potassium obtained at this moment was 4.0 mEq. Because of pain at site of the needle the infusion was stopped and within 4 minutes the bigeminy reappeared *(strip C)*. Reinstitution once again of a rapid infusion resulted in prompt elimination of the bigeminy and appearance of complete A-V dissociation with a ventricular

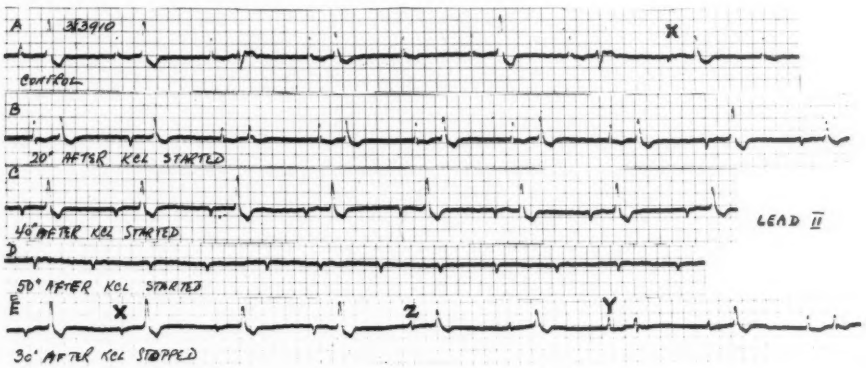

FIG. 4. This figure shows atrial fibrillation with ventricular bigeminy. Infusion of potassium resulted in complete A-V dissociation first with persistence of the ventricular bigeminy (*strip C*) and finally with disappearance of the ventricular ectopic beats. The ventricular arrhythmia reappeared after the infusion was stopped.

rate of 37 beats per minute. The serum potassium level during the A-V dissociation was 4.7 mEq.

Figure 4 (patient 7) shows prior to the infusion *(strip A)* atrial fibrillation and ventricular bigeminy with the third and sixth premature beats differing in appearance from the others. The complex marked *X* is inverted and differs from the dominant complexes marked *Y*. Similar complexes appear in *strips B*, *C*, *D*, and *E*. These beats *(X)* are most likely A-V nodal in origin with aberrant conduction, although their origin below the bifurcation of the bundle of His cannot be ruled out. That the latter may be true is suggested by appearance of complexes marked *Z*, which may represent fusion of *X* and *Y*. If this is the case, then the origin of *Y* must be in ventricles rather than in the A-V node. In *strip B* the *X* beats were more frequent, and in *strip C* they represent the dominant rhythm with resultant complete A-V dissociation and A-V nodal or idioventricular rhythm and ventricular bigeminy. The ventricular premature beats disappeared in *strip D* leaving the A-V node or idioventricular pacemaker in complete control of the ventricles. The ventricular rate of 60 beats per minute is more in keeping with A-V nodal pacemaker rather than one originating below the bifurcation of bundle of His. *Strip E* taken 30 minutes after infusion was discontinued again shows atrial fibrillation with reappearance of the ventricular bigeminy observed during the control period. This experiment stresses again that the disappearance of ventricular bigeminy occurs parallel with marked depression of conduction through the A-V node.

Changes in T Waves and Serum Potassium. Only 3 patients (nos. 2, 5, 6) showed significant change in the amplitude of the T waves. The expected rise in serum potassium at the time the infusion was exerting its maximal effect on the ventricular rate or the cardiac rhythm was not observed. To the contrary, of the 13 patients in whom a satisfactory specimen was obtained during administration of the potassium, 10 showed a serum potassium content lower than that recorded prior to start of the infusion. The drop of potassium level varied from 0.2 to 1.5 mEq., with an average drop for the 10 patients of 0.75 mEq.

DISCUSSION

It is extremely difficult to be certain that a given arrhythmia is due to digitalis and not a result of other factors, even if the patient is receiving digitalis. There are many changes in individuals with heart disease that may give rise to arrhythmias such as are commonly seen in digitalis intoxication. For

example, paroxysmal atrial tachycardia with block, in patients treated with digitalis, is frequently assumed to be a sign of digitalis intoxication. Such a cause-and-effect relation is often difficult to prove. In Barker's[17] early and rather comprehensive review of this arrhythmia one is struck by the paucity of cases due to digitalis, but to the contrary many were abolished by digitalis. The uncertainty that in any given patient digitalis is responsible for the arrhythmia in question is exemplified by our observations. In all our cases the A-V nodal or ectopic ventricular arrhythmias appeared while the patients were under observation and increasing doses of digitalis were being administered. Consequently one can assume that the arrhythmias observed before the infusion of potassium in each case were in some way related to digitalis. If, however, the electrocardiographic changes recorded during our experiments were studied without prior knowledge of administration of potassium, the resultant interpretation would most likely be misleading, because the decrease of conduction through the A-V node, appearance of A-V nodal escape beats, A-V nodal rhythm, and complete A-V dissociation would most certainly suggest to the electrocardiographer increased digitalis effect or digitalis intoxication.

It seems reasonable to assume that if potassium has an effect opposite to digitalis, administration of the former should increase conduction via the A-V node and thus increase the ventricular rate and at the same time abolish the A-V nodal escape beat and escape rhythm. Furthermore, should this occur with concomitant disappearance of ventricular ectopic beats, then one could conjecture that the effect of digitalis was to some extent negated by potassium. Our results, however, failed to bear out this assumption. The ventricular ectopic beats did disappear but with parallel depression of A-V conduction. The latter was manifest by complete A-V dissociation and appearance of an independent ventricular pacemaker. The subsidiary pacemaker was probably A-V nodal in origin with aberrant conduction in one case (fig. 4). This aberrancy, however, cannot be differentiated from beats originating below the bifurcation of the His bundle.

The only conclusion that could be drawn from these observations was that the observed effect of potassium on ventricular rate and ectopic beats must have been one of depression of the myocardium and the A-V node. This depression accounted for disappearance of ventricular ectopic beats, decrease of A-V nodal conduction, and appearance of complete A-V dissociation. Presence or absence of ventricular bigeminy, degree of depression of A-V nodal conduction, and the rate of A-V nodal discharge in presence of A-V dissociation depended largely on the rate of infusion of potassium. In some patients we were able, almost at will, to control the disappearance and reappearance of ventricular bigeminy as well as the degree of depression of the A-V node. The rapidity of changes during the experiment and the reappearance, in less than 30 minutes after infusion was stopped, of the arrhythmias present during the control periods can be best explained on the nonspecific depressing effect of potassium during the infusion. In many cases reported in the literature the dramatic and prompt response to potassium of the arrhythmias occurring in patients under digitalis therapy must have been due to this nonspecific depressing effect. The mechanism of observed alterations is difficult to ascertain. It is unlikely for reasons listed below that the pronounced effect observed in some of our patients could be due entirely to rise in serum potassium. These reasons are (1) the amount injected during any period of "rapid infusion" that resulted in heart block was very small; (2) we were unable to demonstrate any rise in serum potassium at time of maximum depression of conduction but to the contrary in 10 patients there was lowering of the serum level; (3) in only 2 patients did the T-wave change parallel the disturbance of rhythm, but in neither were these changes striking. It is probable, as was pointed out by Wiggers,[14] that the concentration delivered to the heart was greater than that present in the general circulation.

The only evidence suggesting opposite

effect of potassium and digitalis is the late rise in ventricular rate in 8 patients and speeding of A-V nodal rhythm in patient 14. The increased rate of conduction through the A-V node following administration of potassium may have been due to inhibition of the digitalis effect on the node. If this assumption were correct, then administration of atropine at this point, by blocking the vagal effect on the A-V node, should further enhance conduction through the node with a rise of ventricular rate above that observed when atropine was given prior to infusion of potassium. The anticipated speeding of ventricular rate was not observed. Another interesting observation was the relative ease with which complete A-V dissociation was produced in our patients and yet such a state has never been observed in patients with normal sinus rhythm.

It seems that further study of the effect of potassium in atrial fibrillation is needed. Use of larger amounts of potassium and atropine coupled with careful documentation of the rate of infusion and time relation of the observed electrocardiographic changes may clarify the relative significance of the nonspecific myocardial effect of potassium and "antagonism" to digitalis.

Summary

The effect of potassium on the A-V nodal conduction and ectopic ventricular beats in patients with atrial fibrillation treated with digitalis was studied.

The disappearance of ventricular ectopic beats with parallel depression of conduction through the A-V node indicates that the early dramatic response of arrhythmia to intravenous potassium is probably due to a nonspecific myocardial depression.

In all our cases the ventricular ectopic beats present during control period reappeared promptly when infusion was stopped.

The presence or absence of ventricular premature contractions, depression of A-V nodal conduction and the rate of discharge of the A-V nodal pacemaker could often be controlled by merely speeding or slowing the rate of infusion of potassium.

The need for further study of this problem in patients with atrial fibrillation is stressed.

Acknowledgment

We wish to thank Dr. K. G. Kohlsteadt for his continuous support and encouragement and Drs. B. L. Martz and O. M. Helmer for making available to us the laboratory facilities of the Lilly Laboratories for Clinical Research at the Indianapolis General Hospital.

Summario in Interlingua

Esseva studiate le effecto de kalium super le conduction del nodo atrio-ventricular e super le ectopic pulsos ventricular in patientes con fibrillation atrial tractate con digitalis.

Le disparition del ectopic pulsos ventricular con un depression parallel del conduction a transverso le nodo atrio-ventricular indica que le precoce e frappante responsa de arrhythmia al administration intravenose de kalium es probabilemente le resultato de un nonspecific depression myocardial.

In omne nostre casos le ectopic pulsos ventricular que esseva presente durante le periodo de controlo reappareva promptemente quando le infusion esseva arrestate.

Le presentia o absentia de prematur contractiones ventricular, le depression del conduction per le nodo atrio-ventricular, e le mesura del discarga in le pacemaker del nodo atrio-ventricular esseva regulabile in multe casos per simplemente accelerar o relentar le infusion de kalium.

Es sublineate le necessitate de studios additional de iste problema in patientes con fibrillation atrial.

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These 2 enzymes (and transaminase as well) are widely distributed throughout body cells, the former participating in the citric acid cycle and the latter being concerned with glycolysis. Measurement of the plasma level of either enzyme is easy to carry out, although the result in the case of malic dehydrogenase may not be entirely specific. In 18 patients with acute myocardial infarction but not in shock, the plasma activity of all 3 enzymes was abnormally elevated, the peak level of each being reached at about 24 hours after onset of pain. In 14 patients with a variety of liver diseases the plasma activity of all 3 enzymes was elevated in 10 instances, that of 2 of the 3 enzymes was increased in 3 instances, and the activity of all 3 was normal in 1 patient (who had portal cirrhosis). The greatest activity of phosphohexose isomerase and of transaminase was found in patients with infectious hepatitis, whereas peak values of malic dehyrogenase were found in individuals having myocardial infarction. There was fair parallelism in the levels of activity of the 3 enzymes.

Rogers

CLINICAL CONFERENCE

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Polycythemia: A Manifestation of Heart Disease, Lung Disease or a Primary Blood Dyscrasia

By GEORGE N. BEDELL, M.D., RAYMOND F. SHEETS, M.D., HARRY W. FISCHER, M.D., AND ERNEST O. THEILEN, M.D.

DR. GEORGE N. BEDELL: The purpose of this conference is to discuss some of the problems encountered in the differential diagnosis of polycythemia. Polycythemia may be a manifestation of heart disease, lung disease, or a primary blood dyscrasia. Polycythemia vera is a disease of unknown cause. In our hospital we make a diagnosis of polycythemia vera on the basis of finding leukocytosis, high platelet count, and splenomegaly in addition to polycythemia. We require exclusion of conditions capable of producing secondary polycythemia, such as cyanotic heart disease, lung disease, chronic exposure to high altitude, and respiratory center depression. Secondary polycythemia is diagnosed when the patient has polycythemia associated with cyanotic heart disease or lung disease in the absence of leukocytosis, high platelet count, and splenic enlargement. The differentiation of polycythemia vera from secondary polycythemia is sometimes a difficult task. Ratto, Briscoe, Morton, and Comroe[1] have discussed the theoretical reasons that make this distinction possible by measuring arterial oxygen saturation. Also they point out the practical obstacles. The hypothesis is that uncomplicated polycythemia vera should not lead to arterial hypoxemia. No disturbance in pulmonary ventilation, pulmonary circulation, or in the ability of oxygen to diffuse from the alveolus into the red blood cell has been demonstrated in patients with polycythemia vera. If the oxygen saturation of arterial blood is reduced in patients with polycythemia, this suggests that polycythemia is secondary to hypoxemia. This conclusion is questionable because arterial oxygen desaturation may exist from other causes: 1. Patients with polycythemia vera are usually more than 50 years of age. Healthy persons of this age may have slight reduction of arterial oxygen saturation.[2] 2. Patients with polycythemia vera may have concomitant lung disease to account for arterial hypoxemia. 3. Most patients with polycythemia vera whose arterial blood has been studied have no hypoxemia,[1, 3] however, arterial hypoxemia has been reported in polycythemia vera.[4-6] We believe that arterial desaturation in the polycythemic patient is evidence that polycythemia vera exists with another disease or that polycythemia is secondary to another disease.[7] The following cases have been chosen to illustrate how the patient with polycythemia can be studied to evaluate his basic disease.

CASE 1

Mr. C. K., a 49-year-old farmer, was admitted to the University Hospitals on January 6, 1956. He was active and able to do his work until December 1955. At that time, coughing, dyspnea on exertion, and hemoptysis began. His nails had been clubbed since childhood.

The physical examination revealed a white man with clubbing of the fingers and cyanosis of the lips. The blood pressure was 110/78 mm. Hg. The anteroposterior diameter of the chest was increased. The chest was hyperresonant to percussion but the breath sounds were normal. The cardiac rate was 78 per minute and the rhythm was regular. The right heart felt moderately overactive. The pulmonic second sound was extremely loud. There was a grade III systolic murmur in the second and third interspaces to the left of the

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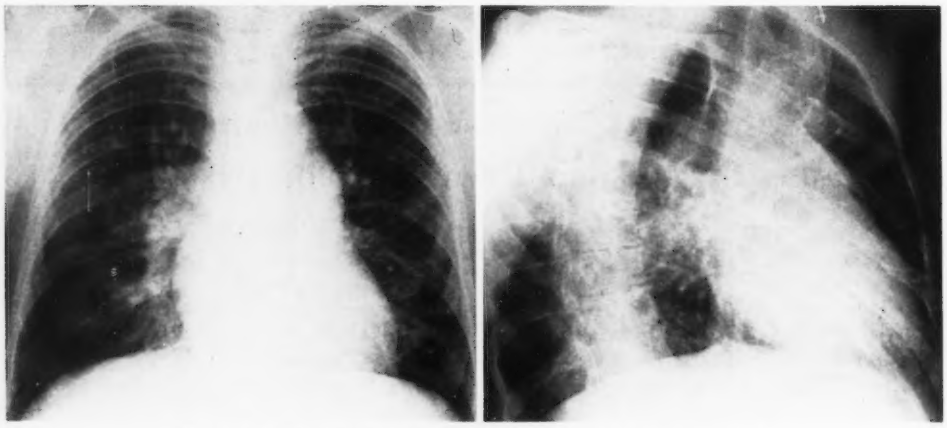

FIG. 1 *Left.* Posteroanterior chest x-ray of Mr. C. K., January 1956.
FIG. 2 *Right.* Right anterior oblique chest x-ray of Mr. C. K., January 1956.

sternum. No diastolic murmurs were heard. The spleen was felt just below the costal margin.

The hemoglobin was 22.5 Gm. per 100 ml., the red blood count was 8.76 million per mm.,[3] and the hematocrit reading was 70 per cent. The white blood cell count was 7,600 per mm.[3] and the platelet count was 134,000 per mm.[3] The electrocardiogram showed right ventricular hypertrophy.

DR. BEDELL: Dr. Fischer, will tell us about the x-rays and cardiac fluoroscopy.

DR. HARRY W. FISCHER: I will comment first of all on the heart itself and then consider the lungs. In this posterior-anterior view of the chest (fig. 1) the heart is just barely enlarged by measurement. It has a Danzer ratio of .51. The striking thing about the appearance of the heart is the very pronounced bulging of the pulmonary artery segment. On the oblique view (fig. 2) the pulmonary artery segment is very prominent. In figure 1 the lung fields show very prominent hilar vessels with an irregular and abrupt attenuation of the vasculature so that the peripheral lung fields are essentially clear and the vascular markings are difficult to see. This attenuation is thought to indicate pulmonary hypertension. The fluoroscopist thought that the findings were suggestive of primary pulmonary hypertension, and that there was no evidence of left-to-right shunt. A search for arteriovenous fistulas was made but were not found at cardiac fluoroscopy.

DR. BEDELL: Pulmonary function studies are recorded in table 1. The lung volumes were normal. The minute volume of ventilation was normal. The per cent nitrogen at the end of 7 minutes of oxygen breathing is a test of the evenness of distribution of inspired air and was normal in this patient. The mechanics of breathing were essentially normal. When the patient's arterial blood was studied it was 78 per cent saturated with oxygen while the patient breathed room air. After he breathed 100 per cent oxygen for 10 minutes his arterial saturation rose to 95 per cent. The normal value for this test is 100 per cent plus 2.00 volumes per cent of oxygen dissolved in the plasma and in the watery parts of the red blood cells. The P_{CO_2} was normal. Failure of the blood to attain full values of oxygenation after breathing 100 per cent oxygen means that some of the arterial blood is flowing from the right to the left side of the heart without passing through pulmonary capillaries which are in contact with ventilated alveoli. When arterial oxygen saturation is as low as 95 per cent after breathing oxygen for a long enough time to wash out nitrogen from the lungs, it nearly always means that right-to-left shunt is present. On the basis of these findings we could not localize the shunt. Our interpretation of the pulmonary function

TABLE 1.—*Results of Pulmonary Function Tests*

	Normal values	Patient C.K.	Patient J.S.	Patient H.H.
Lung volumes				
Vital capacity (ml.)	—	2875	2850	2550
(% of normal)	100	70	52	57
Residual volume (ml.)	—	2900	3790	2200
(% of normal)	100	119	156	196
Ventilation				
Minute volume (L.)	4–6	7.5	9.6	—
Distribution				
% N_2 end 7 min. O_2 (% N_2)	2.5	1.0	9.4	—
Single-breath O_2 test (% N_2)	1.5	—	—	1.0
Mechanics of breathing				
Maximal breathing capacity (L./min.)	—	85	83	99
(% of normal)	100	88	62	84
Maximal expiratory flow rate (L./min.)	400–600	490	100	215
Maximal inspiratory flow rate (L./min.)	400–600	282	147	171
Arterial blood studies				
Breathing air				
O_2 saturation (%)	96–99	78	90	95
P_{CO_2} (mm. Hg)	38–42	41	45	39
Breathing 100% O_2				
O_2 saturation (%)	100+2.00*	95	100+0.94	100+1.34
P_{CO_2} (mm. Hg)	38–42	40	49	40

* Values following + sign refer to ml. O_2 per 100 ml. of blood in excess of that required to saturate hemoglobin (i.e., dissolved O_2).

tests was that they showed normal lung function in the presence of arterial hypoxemia, and evidence of a right-to-left shunt. Therefore an angiocardiogram was done and Dr. Fischer will comment on it.

DR. FISCHER: The angiocardiograms did not show a right-to-left shunt. However, they did confirm the impression of a distorted irregular vascular pattern with abrupt attenuation of the vessels as they left the hilar region. For these reasons the radiologist thought this was primary pulmonary vascular disease with pulmonary hypertension.

DR. BEDELL: The next thing we did to try to localize the shunt was cardiac catheterization. Dr. Theilen, will you describe the findings?

DR. ERNEST O. THEILEN: The cardiac catheter was passed without difficulty into the right branch of the pulmonary artery. The patient had pulmonary hypertension (table 2) with pressures in the pulmonary artery of 116/76 mm. Hg. The mean pulmonary artery pressure was slightly higher

TABLE 2.—*Cardiac Catheterization Findings on Patient C. K., Age 49*

Catheter position	Pressure, mm. Hg		Blood O^2 content vols. %	Saturation %
	S./D.	Mean		
Superior vena cava	—	—	16.4	65
Right atrium	—	7	15.9	63
Right ventricle	121/9	—	16.4	65
Pulmonary artery	116/76	96	19.4	77
Femoral artery (breathing air)	125/75	90	20.5	81
Femoral artery (breathing oxygen)	—	—	24.9	99
Arterial oxygen capacity	—	—	25.2	—

than the arterial mean pressure of 90 mm. Hg. This is not a significant difference. The oxygen content in the pulmonary artery was 3 volumes per cent higher than in the right ventricle. The samples from the right ventricle, the right atrium, and the superior cava were all in the range of 16 to 16.5 volumes per cent, indicating that a left-to-right shunt was not present either at the ventricular or atrial level. He had an abnormal arterial

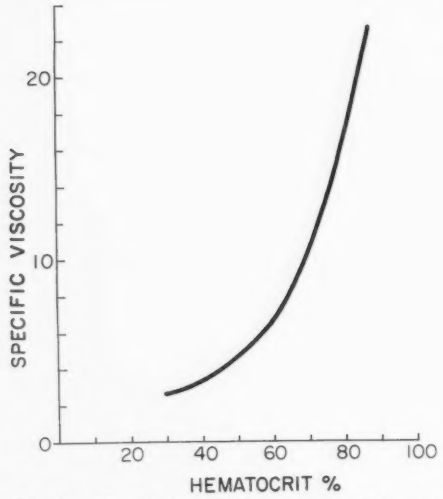

FIG. 3. Correlation of hematocrit with specific viscosity of the blood. *(Reproduced through the courtesy of the author, the W. B. Saunders Company, and the American Academy of Pediatrics.)*

oxygen saturation—81 per cent while breathing room air. Breathing 100 per cent oxygen increased the arterial saturation to 99 per cent. I think the data are indicative of a shunt into the pulmonary artery from the aorta, such as a patent ductus arteriosus. The shunt is bidirectional. There is severe pulmonary hypertension. Ordinarily the treatment of a patient with patent ductus arteriosus is surgical ligation of the ductus. In this patient ligation is contraindicated because of pulmonary hypertension.

DR. BEDELL: This patient has secondary polycythemia. He has none of the diagnostic characteristics of primary polycythemia. His white blood cell count and platelet count are normal. The significance of his palpable spleen is unknown. He had arterial hypoxemia but this has been discussed. At this point I would like to ask Dr. Sheets to discuss the therapy of the polycythemia in this patient.

DR. RAYMOND F. SHEETS: This patient did not seem to be in cardiac failure, so I do not think we have to discuss the ordinary treatment of congestive failure. Polycythemia in this instance is a compensatory mechanism that produces more hemoglobin and red cells so that more oxygen can be carried to the tissues in a given time. I think I can illustrate this briefly. With 14.0 Gm. per 100 ml. of hemoglobin 70 per cent saturated with oxygen the patient has the equivalent of 9.8 Gm. of saturated hemoglobin. When the hemoglobin increases to 22 Gm. per 100 ml. and is only 70 per cent saturated, there is the equivalent of 15.4 Gm. per 100 ml. of hemoglobin that is saturated with oxygen. This actually is not an entirely valid comparison because other factors, such as oxygen dissociation, are involved here, in addition to how much hemoglobin is available to carry oxygen; but I think this gives you the idea of how the compensatory mechanism operates and the reason for it. Difficulty arises after optimal compensation has been made and the regulatory thermostat, which may be erythropoietin stimulated by hypoxemia, fails to stop. Too many erythrocytes are produced. The high viscosity of the blood may overburden the heart and congestive failure may be precipitated. The circulation time may be increased because of the viscosity of the blood so that fewer cells are exposed per unit of time to the respiratory membrane. Consequently the amount of oxygen carried per unit of time will be less than could be carried had not the compensatory mechanism overextended itself. This is illustrated in a recent book by Nadas.[8] The specific viscosity of the blood was measured and plotted against the hematocrit (fig. 3). Note that the viscosity increases abruptly between hematocrit values of 60 and 70 per cent. Dr. Hamilton and I have observed that some patients are worse if the hematocrit is reduced too drastically and they are better when the hematocrit is above normal. Look at the curve. When the hematocrit is greater than 70 per cent the viscosity of the blood increases rapidly and the blood becomes so sticky that it is difficult to propel through the cardiovascular system. The implication of this study is that patients with secondary polycythemia should be bled gradually and slowly to the point where their hematocrit values are between 60 and 70 per cent. The exact point depends on the individual patient. These patients know when they feel

best and that is the place to stop and to hold the hematocrit level. To hold a patient's hematocrit steady is rather difficult. I think it is unwise to use irradiation, either P^{32} or x-rays, to do this because it is difficult to control the dose exactly. If a patient eventually develops iron deficiency from phlebotomies, as is probable, it is necessary to give iron. These patients may develop severe iron deficiency and have little hemoglobin in their cells. When this happens the patient will be pushing around a considerable volume of stroma with little oxygen-carrying capacity. This is illustrated quite well in the case of children as was shown by Rudolph, Nadas, and Borges.[9] Children with congenital cyanotic heart disease are stimulated immediately at birth to produce more red cells. Soon the iron stores are used up and dietary content of iron is inadequate. During this period of rapid growth, production of red cells far outstrips the iron stores and secondary iron deficiency develops. When this occurs, these young children can be benefited by the administration of iron; but then they produce too many red cells, so that phlebotomies are necessary to control the polycythemia.

DR. PAUL M. SEEBOHM: Dr. Sheets, I should like to ask whether or not increased physical activity in the patient who is developing secondary polycythemia in any way influences the degree of the polycythemia. Some patients who live a sedentary life develop this, and others are working vigorously when they develop the polycythemia. Is there any correlation with exercise?

DR. SHEETS: I would guess that there is, but it would be difficult to measure. The reason I believe this is that exercise enhances the degree of hypoxemia. Consequently the erythropoietic stimulus would be great. On the other hand it would be difficult to measure because of the slowness of such a response. The important thing may be the duration of the hypoxemic stimulus throughout the day. In other words, some patients with emphysema may not have secondary polycythemia because they are saturated at rest, which is most of the time, and it is only at certain times when they exercise that they become desaturated.

DR. SEEBOHM: We had better not let that dangle, however, because there are patients with pulmonary emphysema who have hypoxemia at rest and no polycythemia. As a matter of fact this seems to be the rule.

DR. SHEETS: Dr. Seebohm, the time has come when we should do some work on this problem. You and I have batted this question around for a good many years and are fast reaching the point where we are believing our guesses. Several mechanisms have been advanced to explain this, such as blood loss from duodenal ulcer, increased rate of red cell destruction, or failure of the erythropoietic stimulus. Maybe none of these is the explanation.

DR. HENRY HAMILTON: Dr. Bedell, I believe you stated that the lung volumes were normal in this man. Is that correct? What is your range of normal for the vital capacity?

DR. BEDELL: In this patient the vital capacity was 70 per cent of predicted normal. I do not know what the range of normal is; this is probably down some, but I think there is a fairly wide range of normal. I consider 80 to 100 per cent of predicted normal as normal.

CASE 2

Mr. J. S., a 50-year-old coal hauler, was admitted to University Hospitals in August 1952 because of shortness of breath for 2 years, severe occipital headaches for 3 months, and obesity. He had gained weight from 225 to 290 pounds during the 2 years prior to admission. Physical examination revealed a very obese white man in no discomfort. The blood pressure was 164/114 mm. Hg; the pulse rate was 84 and the respiratory rate was 18 per minute. The lips were cyanotic. The chest was symmetrical with equal expansion bilaterally. Moist rales were present over the left base. The left border of cardiac dullness was percussed at the anterior axillary line. No murmurs were heard. The liver was 2 to 3 fingerbreadths below the costal margin. The hemoglobin was 17.8 Gm. per 100 ml., the red blood cell count was 6.03 million per $mm.^3$, the white blood cell count was 9,750 per $mm.^3$, and the platelet count was 180,000 per $mm.^3$ The electrocardiogram was normal.

DR. BEDELL: Dr. Fischer will tell us about the chest x-rays.

DR. FISCHER: These films were taken in

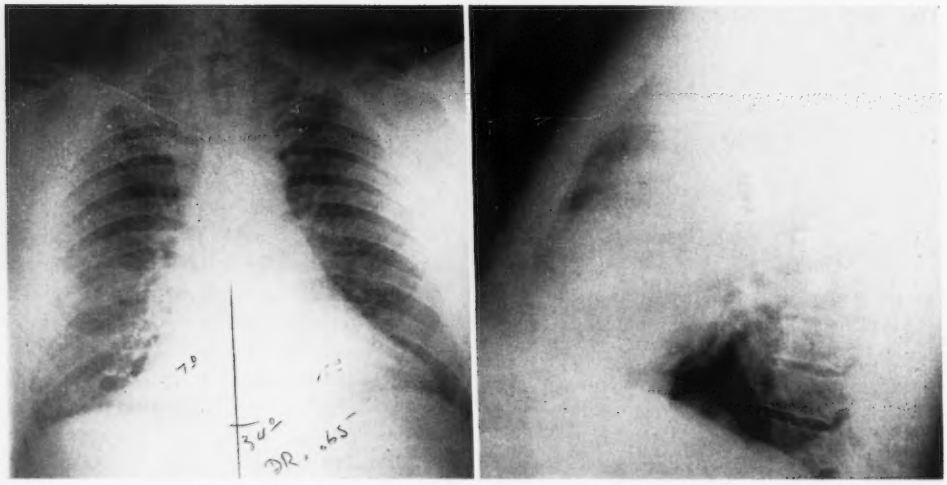

FIG. 4 *Left.* Posteroanterior chest x-ray of Mr. J. S., August 1952.
FIG. 5 *Right.* Lateral chest x-ray of Mr. J. S., August 1952.

August 1952 (figs. 4 and 5). The ratio of the transverse diameter of the heart to that of the chest is .65, which is quite a bit above normal limits. The lungs show some increased markings but their significance is questionable because the patient is extremely obese. Lung markings like these are sometimes seen when the exposure is made through a heavy layer of fatty tissue. It is possible that they could be the result of pulmonary congestion. There is no pleural effusion. There is no increase in the anteroposterior diameter of the chest and no depression of the diaphragm. We were looking for signs of pulmonary emphysema. However, we cannot make this diagnosis radiographically.

DR. BEDELL: The clinical diagnoses were hypertensive cardiovascular disease, obesity, and polycythemia. He was treated with a low-salt, low-calorie diet, digitalis, and mercurial diuretics. Between August 1952 and February 1956 the patient was seen at University Hospitals 7 times. He continued to be overweight. His chief complaint remained shortness of breath on exertion. He continued to work as a coal hauler. During these admissions his red blood cell count ranged between 5.48 and 6.19 million per mm.^{3}, hemoglobin varied from 16.4 to 18.1 Gm. per 100 ml., and the hematocrit ranged from 52 to 65 per cent. The white blood cell count ranged from 7,200 to 12,250 per mm.^{3}, and the platelet count from 138,000 to 180,000 per mm.^{3} X-ray films of the chest were taken on numerous occasions and were interpreted as showing cardiac enlargement but an otherwise healthy chest. Dr. Fischer, would you comment on his chest x-ray taken in 1955?

DR. FISCHER: We have 4 other examinations over a period of about 3 years. All showed cardiac enlargement of varying degrees. The markings of the lungs did not change particularly. The last film, taken in August 1955 (fig. 6), shows essentially the same findings. The heart is smaller than it was on that original film but the lungs look the same. The impression was that this was a healthy-appearing chest for this individual.

DR. BEDELL: At one point this man was seen in the Allergy Clinic because he stated that on exposure to dust from oats and wheat he became very short of breath. Skin tests for the usual inhalants were negative with the exception of house dust, which was slightly positive. The presence of lung disease was always in doubt until 1954, when pulmonary function studies were done (table

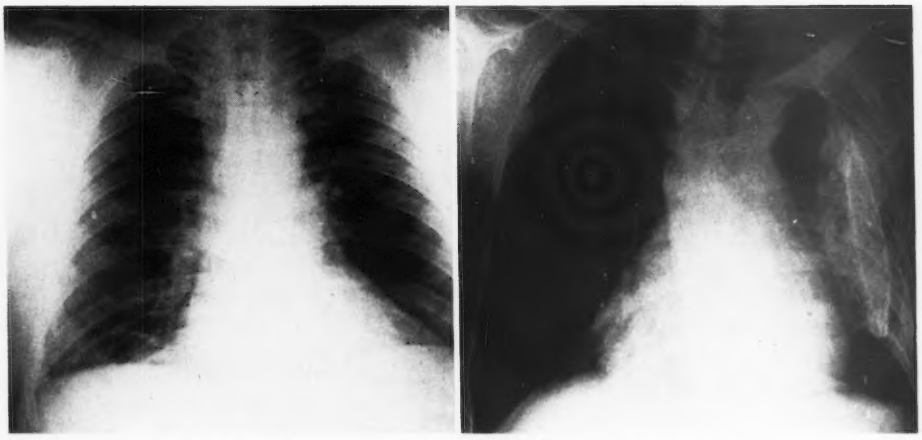

FIG. 6 *Left.* Posteroanterior chest x-ray of Mr. J. S., August 1955.
FIG. 7 *Right.* Posteroanterior chest x-ray of Mr. H. H., February 1957.

1). These show that his vital capacity was reduced to 50 per cent of normal, and his residual volume was increased to 156 per cent of normal. The minute volume of ventilation was normal. The test for distribution of inspired air was very abnormal, 9.4 per cent when it should be 2.5 per cent. The mechanical tests were also abnormal. The maximal breathing capacity and maximal flow rates were reduced, especially the expiratory flow rate, which was reduced out of proportion to the inspiratory rate.

Arterial blood studies showed that while he was breathing room air, his arterial blood was 90 per cent saturated. When he breathed 100 per cent oxygen for 10 minutes, arterial saturation came up to 100 per cent + 0.9 volumes per cent dissolved. He could have had some venous admixture with arterial blood in the lungs, but a right-to-left shunt is effectively excluded as the cause of his hypoxemia. The arterial P_{CO_2} while he was breathing room air was 45 mm. Hg. This is slightly elevated.

The results of these tests are consistent with pulmonary emphysema. During much of the time of observation the clinical diagnosis was polycythemia vera in spite of many normal white blood cell counts and normal platelet counts. After the pulmonary function studies were done, secondary polycythemia was diagnosed. When last seen, in February 1956, his weight was 247 pounds. He was working and clinically he was unchanged. Therapy consisted of bleeding, weight reduction diet (which was not very successful), and occasional mercurial diuretics.

This patient demonstrates some of the problems in diagnosis of polycythemia. Many observers were willing initially to accept the diagnosis of polycythemia vera in spite of the fact that the white blood cell counts and platelet counts were not elevated, the spleen was not palpable, and heart and lung disease had not been excluded completely. At this point I would like to state that it is not unusual for a patient with emphysema to have an essentially normal-appearing chest x-ray. The chest x-ray may be read as "healthy chest" but that is a semantic error. It should be read as "normal-appearing chest x-ray." This does not convey the impression that all types of pulmonary disease were eliminated by the simple procedure of taking a chest x-ray. In the clinical diagnosis of emphysema few signs are present invariably. Increased anteroposterior diameter of the chest or the so-called barrel chest is much talked about, but emphysema can exist without this deformity. A simple useful test is to have

the patient blow his air out as rapidly as possible. If expiration is slow, one may suspect airway obstruction, possibly caused by emphysema. In addition the normal vesicular breath sounds are usually absent, especially over the bases of the lungs. Confirmation of the clinical diagnosis is not difficult. The single-breath oxygen test reveals uneven distribution of inspired air, a hallmark of the disease. The maximal inspiratory and expiratory flow rates give objective evidence regarding the patency of the airways in inspiration and expiration. In typical emphysema the inspiratory flow rate is relatively well maintained, but the expiratory flow rate is severely reduced. Polycythemia is not universally associated with emphysema as Dr. Seebohm has mentioned already. Although polycythemia may be a response to hypoxemia and certainly is in persons with cyanotic congenital heart disease and in persons at high altitudes, the mechanism of this response is unknown and factors that may modify the response are unknown. Ratto et al.[1] pointed out that some patients with severe emphysema may have polycythemia, but this is unusual. They postulate that the polycythemic response is inhibited by chronic infection or perhaps carbon dioxide retention. Dr. Sheets has suggested other mechanisms to explain the absence of polycythemia in the hypoxemic patient with emphysema, namely the possibility of a hemolytic mechanism or bleeding from a duodenal ulcer. As regards therapy of this patient, I think that it is the same as that of the first patient; is that right, Dr. Sheets?

DR. SHEETS: I would like to ask you a question first. What sort of congestive failure do these people with emphysema have? Is it high output failure or low output failure?

DR. BEDELL: Some think it is high-output failure; other people think that it is normal output or low-output failure. I do not believe that this is definitely known.

DR. SHEETS: I suppose that is a good answer. As far as the treatment of the polycythemia itself is concerned, the remarks we made about the previous patient hold in this situation. As far as the treatment of congestive failure in these patients is concerned, one must question the idea that digitalis is not helpful because this is high-output failure. Sometimes digitalis will aid these patients and sometimes it will not. The only way to find out is to try it.

DR. BEDELL: The third case presents a different problem.

CASE 3

Mr. H. H., a 25-year-old station agent, had hemoptysis in 1941. Because of this he was admitted to a tuberculosis sanatorium and diagnosed as having minimal pulmonary tuberculosis. Pneumothorax treatment was complicated by hemopneumothorax. His left lung re-expanded, however, and he was discharged from the sanatorium in November 1945. He returned to work as a station agent and got along well until October 1956, when he developed malaise and increasing nervousness. In November 1956 he suffered a painful blow to the abdomen in a fall from a truck. He was hospitalized because of the possibility that he had ruptured his spleen. Routine blood counts at that time demonstrated polycythemia. His family physician treated the polycythemia with phlebotomies. He suspected that the patient had polycythemia vera and in February 1957 referred him to University Hospitals for treatment with radioactive phosphorus.

Physical examination revealed a thin white man who was alert and cooperative. His blood pressure was 130/80 mm. Hg; the pulse was 90 per minute, and the respirations 20 per minute. The chest was symmetrical. There was a right thoracic, left lumbar scoliosis. The anteroposterior diameter of the left chest was narrow; the right side expanded well and the left side less well. The breath sounds were normal. There were no rales or wheezes. The heart was normal in size. The pulmonic second sound was louder than the aortic second sound. The rhythm was regular. There was a systolic thrill in the third left intercostal space and a grade IV systolic murmur in this area. The hemoglobin was 17.5 Gm. per 100 ml., the red blood cell count was 7.69 million per $mm.^3$, and the hematocrit was 59 per cent. The platelet count was 489,000 per $mm.^3$

DR. BEDELL: Dr. Fischer, will you tell us about his chest x-ray?

DR. FISCHER: I think you can see that this man has considerable chest deformity secondary to the suspected tuberculosis, the

therapeutic pneumothorax and the complicating hemothorax (fig. 7). You didn't say whether or not that was infected, but I suspect that it may have been. This man has a very greatly thickened pleura with deformity of his thorax. The thickened pleura is encroaching upon the left lung. From this we would suspect that perhaps the left lung is not functioning normally. Possibly there is inadequate oxygenation of the blood passing through this lung. The right lung is normal except for the distorted position of the heart. That there is sufficient pulmonary abnormality to interfere with oxygenation is only a suspicion, for even with these pronounced radiographic abnormalities, the patient may have normal pulmonary function.

DR. BEDELL: The results of pulmonary function studies are shown in table 1. The vital capacity was 57 per cent of normal. The residual volume was 159 per cent of normal. The single-breath oxygen test was normal. The maximal breathing capacity was essentially normal; his maximal flow rates were about half of normal. Arterial blood studies were normal. The clinical diagnoses were polycythemia vera, old pleuritis of the left lung with secondary scoliosis, and ventricular septal defect. The patient was treated with radioactive phosphorus.

This man is particularly interesting because he has polycythemia vera, lung disease, and heart disease. In this patient the diagnosis of polycythemia vera rests on solid ground. He has a high red blood cell count, hemoglobin, hematocrit, white blood cell count, and platelet count. He has a palpable spleen and normal arterial oxygen saturation. His lung disease has not produced arterial hypoxemia. Dr. Sheets will discuss the decision regarding therapy in this patient.

DR. SHEETS: This man is asymptomatic at the present time—his polycythemia was discovered when he fell off a wagon and hit his belly on the sideboard. At that time he had a big spleen and the diagnosis of polycythemia vera was made. Either horn of the dilemma that occurs in polycythemia vera may cause difficulty. On the one hand, these patients develop vascular thromboses, which are troublesome, and on the other hand they bleed excessively, which gets them into difficulty. Much of the therapy is directed at alleviating these 2 conditions in addition to the trouble caused by too many red cells. In this hospital Dr. Fowler and Dr. Hamilton have obtained good control of many of these patients with phlebotomy only. Some patients can be bled once every 6 months or so and maintain a relatively normal hematocrit. Eventually if they become deficient in iron, so that their hemoglobin concentration is grossly below their red cell count, their diet should be supplemented with iron so that the red cells which they circulate are normal in hemoglobin content. Finch, Haskins, and Finch,[10] who studied the treatment of polycythemia vera with phlebotomy thought that one of the mechanisms of control of this disease with phlebotomy was to make the patient deficient in iron. It takes about 6 months of frequent, repeated bleedings to make many of these patients deficient in iron and it will not control the red cell production in all patients. When it does not, those who are deficient and continue to make cells will have a high volume of red cells as measured by hematocrit, although they may have a very low hemoglobin. This patient at one stage in his treatment was in such a situation. The other important factor in the patient with polycythemia vera is the platelet count. This man's was fairly high—489,000 per mm.^{3} In this hospital the normal is 100,000 to 150,000 per mm.^{3} Some patients have platelet counts of 2 to 3 million per mm.^{3} Phlebotomy will not control the platelet count and one must use radiation to do this. It seems to make very little difference whether one uses x-ray or P^{32} as far as the final result is concerned. At the present time P^{32} is used in most hospitals. The total dose is around 9 millicuries. This dose was established in a study by Lawrence et al.[3] If one were seeing a patient for the first time, the initial dose of P^{32} would be

given immediately, followed in 3 or 4 days by phlebotomies to reduce the red blood cell volume. Three months later evaluation would be made to determine the rate at which red blood cells and platelets had reformed. Another dose of P^{32} might be given at that time.

DR. I. MCLEAN SMITH: Do patients with polycythemia vera get leukemia more often than patients with secondary polycythemia?

DR. SHEETS: The incidence of leukemia in secondary polycythemia is the same as in the ordinary population, but it is somewhat higher in polycythemia vera.

DR. HAMILTON: Dr. Bedell, did this patient have proved pulmonary tuberculosis?

DR. BEDELL: No, it was not bacteriologically proved but apparently the x-rays were compatible with it.

DR. HAMILTON: Is is possible that the patient had a thrombosis of the pulmonary vessels from polycythemia to give that picture?

DR. BEDELL: It seems a long time—it was almost 15 years. He was in the tuberculosis hospital in the early 1940's and then his polycythemia was discovered in 1955.

DR. HAMILTON: I would like to call to your attention the fact that the platelet count may rise long before the hematocrit does, heralding polycythemia vera even when asymptomatic.

DR. BEDELL: We have discussed 3 patients with polycythemia. I can summarize the conference with the following statements.

Patients with polycythemia vera usually have high white blood cell counts, high platelet counts, and palpable spleens, but this is not always so. Arterial oxygen saturation during the breathing of room air is normal in every patient with uncomplicated polycythemia vera. Patients with secondary polycythemia have an elevated red blood cell count, hemoglobin, and hematocrit in the absence of leukocytosis, increased platelets, or splenomegaly. All have arterial hypoxemia. Although the presence of heart or lung disease is not always apparent immediately, careful physiologic evaluation usually will disclose the mechanism producing hypoxemia.

Treatment in patients with this disease must be individualized. We believe that some patients with polycythemia vera can be treated with phlebotomy alone. When patients with polycythemia vera have high platelet counts this is considered an indication for irradiation, with either x-ray therapy or radioactive phosphorus. We recommend that patients with secondary polycythemia be bled to the point where their hematocrit is around 65 per cent.

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CLINICAL PROGRESS

Transposition of the Pulmonary Veins

By WARREN G. GUNTHEROTH, M.D., ALEXANDER S. NADAS, M.D., AND ROBERT E. GROSS, M.D.

PULMONARY veins entering the right atrium or its tributaries constitute the entity of transposition of the pulmonary veins. The transposition may be complete, when all the veins enter the right heart, or incomplete, when only some of the pulmonary veins drain anomalously. We are reviewing our experiences with total and partial anomalies of pulmonary venous drainage because of the increasing surgical interest in the problem, and because we feel that the clinical profile to be presented is sufficiently characteristic to enable the cardiologist to make the diagnosis with relative ease in most instances.

MATERIALS AND METHODS

Thirty-one patients with uncomplicated transposition of the pulmonary veins admitted to the Children's Medical Center in Boston, were studied clinically, with complete history, physical examinations, x-ray and fluoroscopic examinations, and 12-lead electrocardiograms. The diagnosis was confirmed in each instance by cardiac catheterization, surgery, or autopsy. The technics used in our cardiac catheterization laboratory have been described in previous publications.[1]

COMPLETE TRANSPOSITION OF THE PULMONARY VEINS

Definition

Drainage of the entire systemic and pulmonary return into the right heart is the major abnormality in complete transposition of the pulmonary veins. An atrial septal defect or a patent foramen ovale is necessary for any systemic output, and is therefore an integral part of the lesion. Following Brody's original classification,[2] we have not considered a patent ductus arteriosus as a complicating anomaly, but have excluded cases with other major cardiovascular abnormalities from discussion here.

Incidence

Complete transposition of the pulmonary veins is a rare condition. Maude Abbott[3] found only 4 cases (including 3 complicated ones) in her series of 1,000 autopsies of congenital heart disease. Brody, in a classical monograph in 1942,[2] reviewed 38 cases from the literature; 14 of these were associated with other major cardiac anomalies. Up to the present time there have been 159 uncomplicated cases reported.[4-11]

Embryology

The developmental anomaly producing this malformation probably occurs in the seventh week of gestation[12] and represents either complete failure of absorption of the common pulmonary vein into the dorsal wall of the sinus venosus, or abnormal placement of the ostia of this vein in relation to the septum, which divides the sinus venosus into the right and left atria. In the first instance, the pulmonary veins drain via a persistent, enlarged primitive connection between the pulmonary and systemic circulations. These connections have been demonstrated in normal adults with postmortem injections by Zuckerkandl in 1881, and are reminiscent of the development of the entire pulmonary circulation from part of the presplanchnic plexus.[13]

Anatomic Considerations

The site at which the pulmonary veins connect to the systemic circulation has been used as the basis of anatomic classification of complete transposition of the pulmonary veins by Darling, Rothney, and Craig.[4] This

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TABLE 1.—*Classification[4] and Incidence of Types of Complete Transposition of the Pulmonary Veins, Based on 159 Uncomplicated Cases*

Level of drainage	Type	Percentage	
Supracardiac	IA left superior vena cava	48%	57%
	IB right superior vena cava	9%	
Cardiac	IIA coronary sinus	14%	32%
	IIB right atrium	18%	
Infracardiac	III portal vein or ductus venosus		9%
Mixed levels	IV		2%

classification has considerable interest for prognostic and surgical reasons. We have classified 159 uncomplicated cases from the literature according to this method (table 1).

Certain other anatomic considerations are of surgical importance. The anomalous veins, with great consistency, form a relatively large common channel prior to joining the systemic veins except when they join the right atrium directly. In the latter group approximately one third join the right atrium by multiple channels, but more than one half empty into an ante-chamber, described by Kirchmair and Blum,[14] which is, from the surgeon's point of view, conveniently located on the posterosuperior wall of the right atrium, to the left of the superior vena cava and inferior vena cava, and superior to the coronary sinus and the atrioventricular conduction system.

Finally the entire left heart is relatively hypoplastic; and, as Keith pointed out,[15] the circumference of the common pulmonary vein frequently exceeds that of the waist of the left atrial appendage, a formidable disadvantage in attempting surgical correction of this condition.

Physiology

Complete transposition of the pulmonary veins is a serious anomaly, profoundly altering the normal circulatory pattern. In this anomaly, the right atrium receives the entire systemic and pulmonary venous return, and supplies the left heart through a patent foramen ovale or an atrial septal defect. As in other types of congenital heart disease with complete mixing, the systemic arterial saturation will depend entirely on the ratio of pulmonary to systemic flow, at a given oxygen consumption.*

However, as various investigators have pointed out,[8, 16] mixing at the atrial level may not be complete. The systemic arterial saturation is often slightly less than that of the pulmonary artery; this difference is attributed by the Mayo group[16] to preferential shunting of the inferior vena caval blood through the interatrial communication. This type of preferential shunting has a precedent in fetal circulation.[17, 18] Occasionally, the pulmonary artery oxygen saturation is lower than that of the systemic artery, perhaps due to preferential flow of blood from the coronary sinus or superior vena cava across the tricuspid valve into the right ventricle.

Although the resting systemic output of these patients is usually normal or only slightly reduced, increasing output 3 or 4-fold (as with moderately severe exercise) would require a corresponding increase in pulmonary blood flow, if the systemic arterial saturation were maintained. With a resting heart rate greater than average and a right ventricular stroke volume 2 to 3 times that of the left, the required pulmonary blood flow would be almost impossible to achieve. Evidence of the resultant limitation of cardiac output is the almost universal history of easy fatigability and the autopsy finding of a hypoplastic left heart.

Although the majority of patients with complete transposition of the pulmonary veins die in infancy or early childhood, a few survive into adulthood with remarkably few symptoms. How this group maintains a compensated cardiovascular system in the face of such profound disorder has never been explained satisfactorily.

Presentation of Data

Clinical Material

Twenty patients with uncomplicated, com-

*Dow[19] and Burchell[16] have recently derived formulae to predict the systemic arterial saturation on the basis of these parameters.

plete transposition of the pulmonary veins have been studied at our hospital in the years 1950 to 1956. Because the clinical picture may vary considerably, depending upon the level at which the pulmonary veins drain, we have used Darling, Rothney, and Craig's classification[4] to subdivide our material. The pulmonary veins drained into an ascending left superior vena cava in 9 of our cases, into the coronary sinus in 4, into the right atrium in 3, and below the diaphragm in 4 patients.

The clinical diagnosis was confirmed by operation or autopsy in 15 patients,* and by cardiac catheterization only in the remaining 5.

Our patients ranged in age from 10 days to 19 years with an average age of 5 years; 10 of them were less than 6 months old. The group draining below the diaphragm was unique in that none survived more than 7 weeks and 2 survived only 10 days. None of the others died at less than 7 weeks of age.

The incidence of males in the entire group was the same as females; in the infradiaphragmatic group, all 4 patients were males.

The interatrial communication in the 12 autopsied cases was a patent foramen ovale in 10 instances, and an atrial septal defect in 2 (1 ostium primum and 1 ostium secundum). The size of the interatrial opening in our autopsied cases had no correlation with longevity or degree of unsaturation when taken in relation to the circumference of the mitral valve (table 2). Previous reports attributing prognostic importance to the size of this opening failed to correlate it with the over-all heart size.

Similarly, the presence and size of a patent ductus arteriosus had no correlation with longevity in our patients. Eight of the 12 autopsied cases had patent ducti, probe-patent in 5, moderate sized in 1, and large in 2.

Mild pulmonary vascular obstruction was found in 5 autopsied patients, and moderate obstruction in 4. Although the 3 patients in the autopsied group surviving the longest had no obstructive changes, there was no correlation, in the other 9 patients, of age at death with severity of medial hypertrophy and intimal hyperplasia of the pulmonary arteries.

TABLE 2.—*Correlation of Age of Death with Size of Interatrial Communication and Patency of Ductus Arteriosus*

Age	Type	Degree cyanosis	Circumference ASD or PFO (cm.)	Circumference mitral valve (cm.)	Ductus
10 days	III	3+	2.8	3.0	Large
10 days	III	1+	2.5	3.0	Closed
6 weeks	III	1+	4.7	3.0	Probe patent
7 weeks	III	1+	5.5	3.5	Closed
2 months	I	2+	1.5	3.0	Large
2 months	I	1+	1.5	3.7	Probe patent
2 months	I	2+	.6	3.5	Closed
3 months	I	1+	1.5	3.5	Probe patent
4 months	IIA	1+	3.9	4.0	Closed
*1⅔ yrs.	IIB	1+	5.5	5.5	Probe patent
*1⅔ yrs.	I	1+	3.1	5.0	Moderate size
*4⅔ yrs.	I	2+	2.4	5.0	Probe patent

* Operative deaths.
ASD = atrial septal defect.
PFO = patent foramen ovale.

History

There was no family history of congenital heart disease in any of our 20 patients. In 4 instances, however, there were difficulties in the first trimester of pregnancy; 2 "viral" respiratory infections, 1 threatened abortion, and 1 instance of severe malnutrition.

The symptoms presented by these patients were nonspecific; mild cyanosis, fatigability, dyspnea, and increased frequency and severity of respiratory infections were almost universal complaints. The onset of cyanosis varied from birth to 12 years of age. Squatting and "anoxic" spells were relatively uncommon, occurring in one fifth of the patients.

Physical Examination

The findings at physical examination were more specific, in certain instances, than were the histories of these patients. The patients were small and undernourished in general; over two thirds of them fell below the twenty-fifth percentile on our height and weight charts.[20]

*The autopsy material of the Children's Medical Center has been presented in detail in an earlier publication.[4]

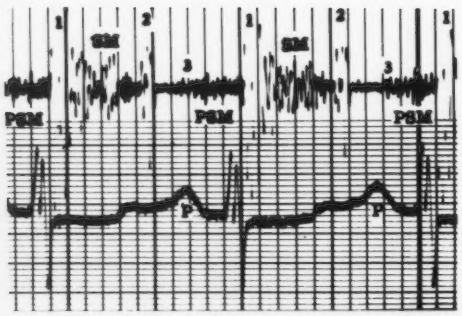

FIG. 1. Phonocardiogram in complete transposition of the pulmonary veins, illustrating the multiple heart sounds, and systolic and presystolic murmurs.

The patients without exception were at least mildly cyanotic; more marked cyanosis was found in the group with congestive failure, and in the group with drainage below the diaphragm. Only one half of the patients demonstrated clubbing.

The resting pulse rate was above normal range in 14 patients, including 11 in congestive failure. The blood pressure and pulse pressure did not vary significantly from the normal.

Congestive failure was diagnosed in 16 of 20 cases, manifested in every instance by a large liver, but in only half by distended veins or peripheral edema. Hepatomegaly was particularly marked in the patients with drainage below the diaphragm. The presence of pulmonary congestion was difficult to ascertain by physical examination alone, because of the high incidence of concomitant respiratory infections. In 1 case with drainage into the portal vein, pulmonary edema was diagnosed clinically and radiologically and was confirmed at autopsy.

Left chest prominence was found in 8 of the older children with very large hearts. In every instance, the cardiac impulse was maximal at the lower left sternal border.

On auscultation, the first sound was loud at the apex or lower left sternal border in 6 cases; the second sound was increased in intensity at the pulmonic area in one half the cases, and within normal limits in the remainder. Splitting of the second sound was observed in all but 2 patients. An unusually prominent third sound was present in 13 of 20 patients, and a fourth, or atrial sound was audible in 5 patients.

Systolic murmurs were heard in all except 2 patients, who were 6 and 8 weeks of age respectively. The systolic murmurs were usually soft and heard best at the left sternal border, the majority being maximal at the fourth interspace, but only slightly fewer at the second to third interspaces. This type of soft systolic murmur has been attributed to tricuspid insufficiency by Keith.[15] A palpable systolic thrill and rough, loud murmur were noted in 5 patients; 4 of these were found to have a pressure gradient across the pulmonic valve, and in the fifth, catheterized from the femoral vein, the pulmonary artery was not entered.

Eleven patients had low frequency mid-diastolic murmurs at the apex or lower left sternal border. This type of murmur, frequently found in patients with a large ventricular stroke volume,[21] was observed in every patient over 6 months of age. A presystolic murmur of medium to high frequency at the lower left sternal border, synchronous with atrial systole, was heard in 6 instances (fig. 1). This murmur was usually diamond shaped on the phonocardiogram, and was accompanied by a fourth sound. Examples of this murmur were heard in all types except the group with subdiaphragmatic drainage; within the framework of the other clinical features, we consider its presence to be practically pathognomonic.

Keith and associates[15] have described a pronounced, although transient, venous hum at the upper left sternal border in 4 patients with drainage of the pulmonary veins into a remnant of the left superior vena cava. We were able to find this type of murmur in only 1 case, and then the murmur was maximal at the right sternal border.

Electrocardiograms

The electrocardiograms of patients with complete transposition of the pulmonary veins reflect the pathologic physiology and anatomy, with evidence of right-sided hypertrophy and dilatation. Right axis deviation, right ventricular hypertrophy, and incom-

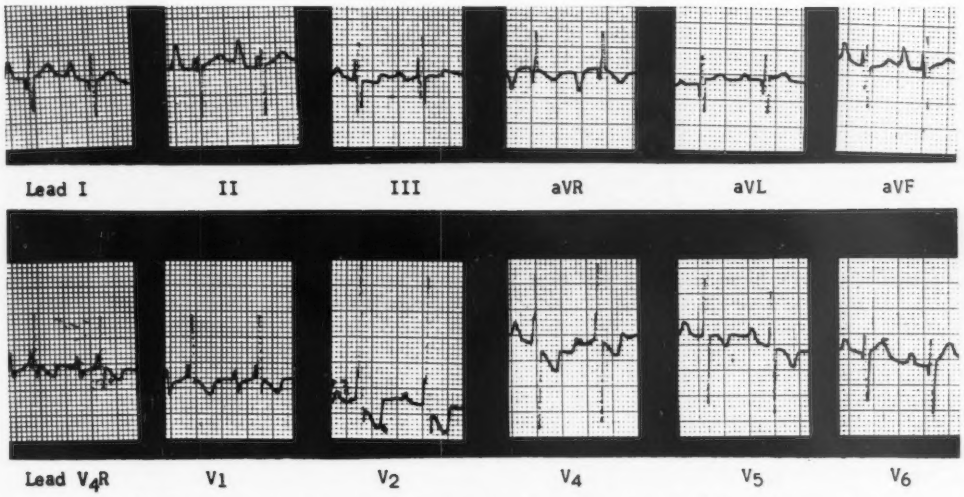

FIG. 2. Representative electrocardiogram in complete transposition of the pulmonary veins, illustrating marked right ventricular hypertrophy, incomplete right bundle-branch block, P pulmonale, and T-wave changes.

plete right bundle-branch block were present in every patient (fig. 2). The degree of right ventricular hypertrophy in this group of patients is marked and has been noted by others. Although Keith and co-workers[15] emphasized the frequency of a qR pattern in the right precordial leads, we found this pattern in only 5 cases; and in these there was evidence suggesting that the pattern was actually an rsR′ pattern, with an isoelectric r. A more frequent finding in our series was complete reversal of the adult R/S progression in the precordial lead, i.e., qR, rsR,′ or Rs pattern in the right precordial leads, and qrS in the left precordials, indicating marked right ventricular hypertrophy.[22] Sixteen of our patients demonstrated this phenomenon, and the exceptions were all in the older age group.

Right ventricular intrinsicoid deflection delay correlated closely with age, but was abnormally delayed in 15 cases. The group draining below the diaphragm were an exception, with 3 out of 4 having a normal activation time, which may be correlated with the relatively small size of their hearts by x-ray and postmortem examination.

T-wave abnormalities occurred in 13 cases. An additional 3 cases had T-wave abnormalities, possibly due to digitalis.

FIG. 3. Radiogram of patient with drainage of all pulmonary veins into an ascending left superior vena cava illustrating the figure-eight pattern.

A tall, peaked P wave, or P pulmonale, was present in 13 of 20 cases. In the 4 patients with drainage below the diaphragm, there were no instances of P pulmonale.

X-Rays

The radiograms of certain types of complete transposition of the pulmonary veins are practically pathognomonic, as for exam-

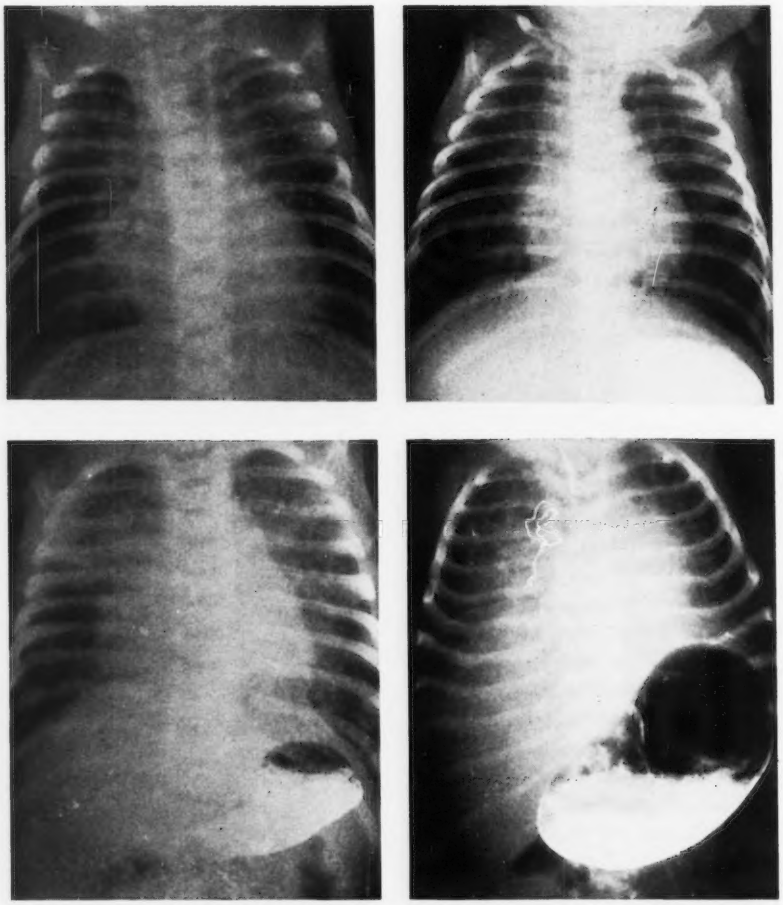

FIG. 4. Radiograms of 4 patients with drainage of all pulmonary veins into the portal vein, illustrating a small heart in the presence of intense pulmonary congestion and hepatomegaly.

ple the figure-eight pattern described by Snellen and Albers[23] (fig. 3). The upper half of the 8 is formed by a remnant of the left superior vena cava, as it ascends to join the left innominate, and the right superior vena cava emptying caudally into the right atrium. This venous structure will pulsate, if at all, in an "acv" pattern, whereas the pulmonary artery will expand synchronously with ventricular systole. The thymus, in the upper, anterior mediastinal area, does not pulsate intrinsically at all. A wide superior mediastinal pattern also may be produced by a true, persistent left superior vena cava without pulmonary venous anomaly, as it descends to drain into the coronary sinus; this group lacks, however, the rounded upper margin characteristic of the figure-eight, and the patients are not ordinarily cyanotic. The full-blown figure-eight pattern is not usually found in infancy. The youngest patient in our series with this contour was 4 years old, although in every case over the age of 3 months, widening of the superior mediastinum was definite.

The group with drainage below the diaphragm also presents a pathognomonic roentgenologic picture of moderate to marked pulmonary vascular engorgement and congestion with a normal-sized heart (fig. 4). There is

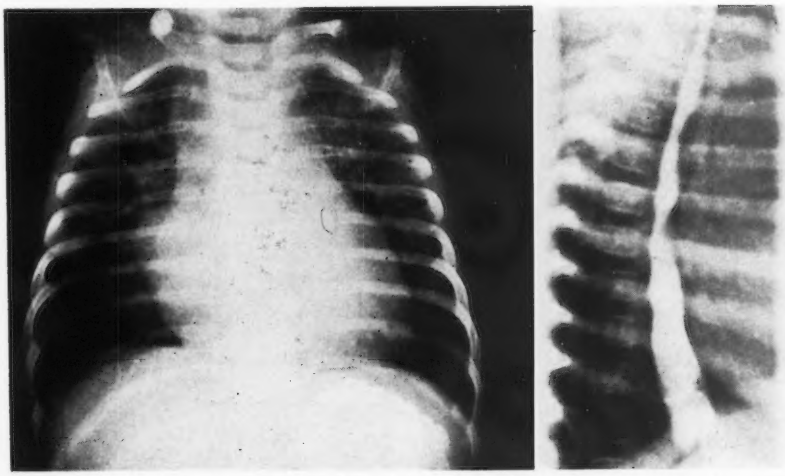

FIG. 5. Radiogram of a patient with drainage of all pulmonary veins into the coronary sinus: Postero-anterior film of chest and lateral view of barium swallow. *(Reproduced from Nadas, A. S., Pediatric Cardiology, Philadelphia and London, W. B. Saunders Company, 1957, page 518.)*

no other type of cyanotic congenital heart disease demonstrating this combination, in the presence of congestive failure. However, the vascular pattern per se is not different from that seen in other heart diseases in which there is passive congestion, such as mitral stenosis.

When drainage occurs at the atrial level, the radiogram is nonspecific in most instances. Two of 4 cases with pulmonary return into the coronary sinus had a widened superior mediastinal shadow due to a true left superior vena cava, which also drained systemic blood into the coronary sinus. One of these patients had a bulge in the posterior aspect of the cardiac shadow, on barium swallow, suggesting by its size and location an enlarged coronary sinus (fig. 5). Another patient with drainage into the coronary sinus had an angular prominence of the upper right atrial border, directly across from the sinus ostium. When the veins drain directly into the right atrium, the picture is characteristic only of the basic disorder (fig. 6). The cardiac silhouette produces a box-like shadow, as Gott et al.[6] pointed out, but so do most lesions involving the right side of the heart with increased pulmonary blood flow.

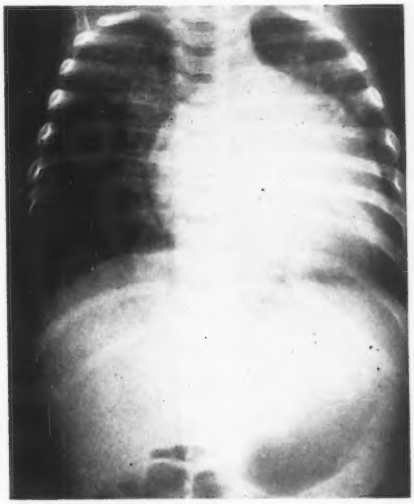

FIG. 6. Radiogram of a patient with drainage of all pulmonary veins into the right atrium, illustrating a "box-like" pattern.

Cardiomegaly was present in our 20 patients in every instance except for the 4 cases with drainage below the diaphragm. In the majority of cases, the enlargement was moderate to marked. In the cases where congestive failure had not obliterated the character-

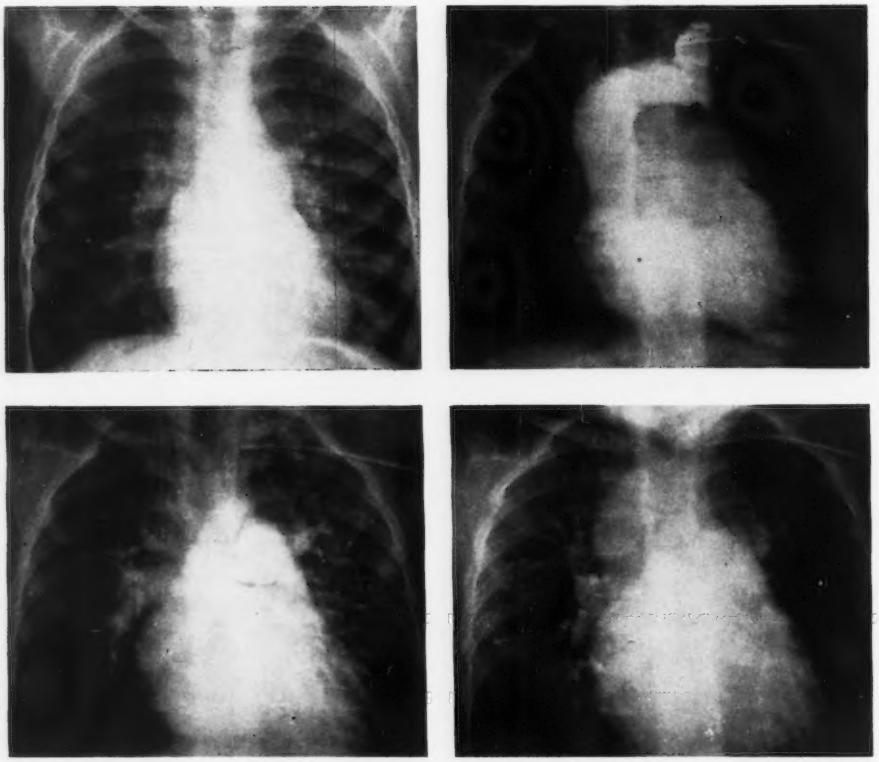

FIG. 7. Venous angiocardiogram in a patient with drainage of all pulmonary veins into an ascending left superior vena cava, outlining the supracardiac vascular pattern formed by the left cava, left innominate, and right superior vena cava. *(Reproduced from Nadas, A. S., Pediatric Cardiology, Philadelphia and London, W. B. Saunders Company, 1957, page 521.)*

istic contour, right ventricular configuration was uniformly present. Atrial enlargement could be diagnosed with certainty in 9 patients; there was no demonstrable atrial enlargement in any of the cases draining below the diaphragm. The pulmonary artery was abnormally prominent in over one half, and pulmonary vascular engorgement was marked in all. Passive congestion was present in over half of the children, including all of those with drainage below the diaphragm, in whom it was particularly marked. "Hilar dance" or intrinsic pulsation of the hilar vessels, was found in 8 of the 20 cases, and its absence was correlated in every instance but 1 with an age of less than 6 months.

Angiocardiograms were performed in only a small number of our cases (fig. 7). Since a definitive diagnosis can be made without angiocardiographs, the additional risk of this procedure is not justified, in our opinion, except in those cases being considered for cardiac surgery when additional anatomic detail is desired; and then, it should be done by selective angiocardiography. By venous angiocardiography, however, the exact site of union was never established, when it was not known with certainty prior to the procedure.

Cardiac Catheterization

We have catheterized 10 patients with complete transposition of the pulmonary veins, including 4 patients with drainage into the superior vena cava, 3 draining into the coronary sinus, and 3 into the right atrium, (table 3). None of our 4 cases with drainage below the diaphragm was catheterized (none

TABLE 3.—*Data from Cardiac Catheterization of Patients with Complete Transposition of the Pulmonary Veins*

Patient number	1	2	3	4	5	6	7	8	9	10
Type	I	I	I	I	IIA	IIA	IIA	IIB	IIB	IIB
Age (years)	2	4	15	19	7	10	12	5/12	2	19
Rise in O_2 at level of mixing (vol. %)	4.8	5.2	3.9	4.6	3.4	4.7	5.1	4.3	4.3	5.5
(% saturation)	26	26	21	23	15	25	29	29	27	25
Systemic artery (% saturation)	80	84	93	88	85	87	93	47‡	88	87
Pulmonic artery (% saturation)	82	84	89	87	84	86	92	51	88	87
Systemic index (L./min./M.²)	6.6	3.2	6.3	2.9	4.7	3.3	2.6	3.9	5.1	2.3
Pulmonic index (L./min./M.²)	6.6	6.7	15	7.5	4.7	5.8	11	2.4	11	10
Resistances ratio (Pulm/Systemic)	*	1/20	1/7	1/7	*	*	1/37	*	1/11	1/32
Wedge pressure (mm. Hg)	2†	—	—	—	—	—	—	—	—	12
Rt. atrial pressure (mm. Hg)	3	3	6.5	10	3	9	9	15	5	12

* These patients were catheterized from the femoral vein and the pulmonary artery was not entered.
† Actual left atrial pressure.
‡ Probably not representative. This patient's condition deteriorated markedly during the procedure.

survived beyond 7 weeks). The ages of the catheterized subjects ranged from 6 months to 18 years with an average age of 9 years.

Arterial oxygen saturation ranged from 80 to 93 per cent with an average of 87 per cent. (This range excludes 1 patient whose condition deteriorated during the procedure, whose saturation was 47 per cent.) The rise in oxygen saturation at the site of union of the systemic and pulmonary returns, varied from 15 to 29 per cent with an average of 25 per cent. The resting cardiac output ranged from 2.3 to 6.6 L. per minute per M.² of body surface area, with an average of 3.9 (within normal limits for resting cardiac index). Pulmonary blood flow, however, ranged from 4.3 to 15 L. per minute per M.², with an average of 8.7. The average ratio of pulmonary to systemic flow, thus, was 2.2 to 1. Although literally all of the systemic flow was via a right-to-left shunt at the atrial level, the effective right-to-left shunt (i.e., the dilution of oxygenated blood with unsaturated venous return) was small relative to the left-to-right shunt. This ratio, on the average was 1 to 7.*

Right atrial pressures were somewhat increased, on the average, although there was considerable spread, 3 to 15 mm. Hg. In 1 patient the left atrium was entered and was found to have a mean pressure of 1 mm. of Hg less than the right atrium. Pulmonary artery wedge or "P.C." pressure was obtained in 1 patient and was identical with the right atrial pressure. There was no close correlation between the clinical manifestations of failure and the right atrial pressure. For the patients not in congestive failure, there was an interesting inverse relationship between right atrial pressure and *left* ventricular output; the higher the right atrial pressure, the lower the systemic output (fig. 8). With patients in failure there was somewhat more scatter, but the trend persisted. In the patient with marked deterioration during the procedure, the highest right atrial pressure was obtained; and the relationship to cardiac output was considerably out of line with the other 9 patients. This relationship, although based on a relatively small number of cases and subject to the serious limitation of calculating outputs, has previously been described by Dow and Dexter[24] in patients with atrial septal defects. Dow and Dexter suggested that peripheral tissue requirements determine left ventricular output, which in turn determines the left atrial pressure, and finally, the right atrial pressure, since these 2 chambers have nearly identical pressures in patients with large atrial defects.*

Mild gradients across the pulmonic valve

*Systemic flow, in addition to pulmonary flow, is difficult to estimate with accuracy in these patients, since obtaining a true mixed venous sample is impossible.

*This relationship does not contradict the findings of Goodale et al.[25] in similar cases, where there was a direct relationship between right atrial pressure and right ventricular stroke work.

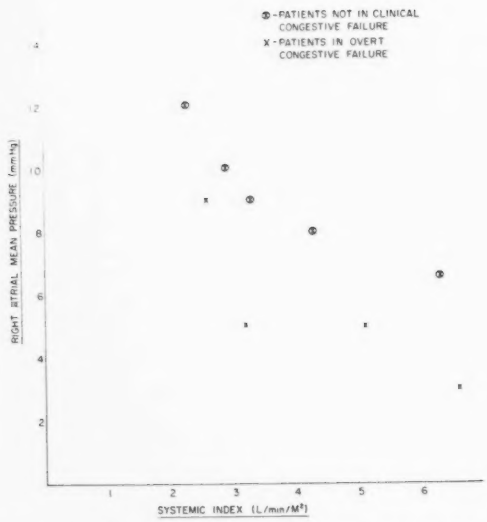
⊕-PATIENTS NOT IN CLINICAL CONGESTIVE FAILURE
X-PATIENTS IN OVERT CONGESTIVE FAILURE
RIGHT ATRIAL MEAN PRESSURE (mm Hg)
SYSTEMIC INDEX (L/min/M²)

FIG. 8. Graph of the relationship of right atrial pressure to left ventricular output in patients with complete transposition of the pulmonary veins.

ranging from 4 to 17 mm. were observed in 4 patients. All of these had palpable thrills on physical examination.

Although half of our catheterized patients were in frank congestive failure, the calculated pulmonary vascular resistance was not markedly increased in any, with the average ratio of pulmonary to systemic resistance of 1 to 12, the highest being 1 to 7. This is in contradistinction to Burchell's theory that the main factor causing heart failure is the effort of the right heart to maintain a high flow of blood against increasing pulmonary resistance.[9] Similarly, all 13 autopsied cases showed evidence of congestive failure, but only 4 showed severe pulmonary vascular obstruction, and 5 showed only slight changes.

Surgery

Surgical correction of complete transposition of the pulmonary veins was attempted in 3 instances between January 1954 and January 1957 at the Children's Medical Center. The first patient was a 4-year-old girl with all pulmonary veins draining into the left superior vena cava. An anastomosis was created between the common pulmonary vein and the posterior wall of the left atrium, in a horizontal fashion, paralleling the atrioventricular ring. The ascending portion of the left superior vena cava was then ligated and divided. The patient developed pulmonary edema, apparently caused by the inadequate size of the left atrium and ventricle, and death followed within 2 hours. Similar experiences have subsequently been reported by others.[15, 26] The second patient, an 18-year-old girl with the same anatomic abnormality was operated upon in the same fashion, except that the left cava was not divided, but constricting stitches were placed to reduce the lumen to approximately one fifth of its previous diameter (fig. 9). A 2-stage operation was planned with complete division of the ascending cava to be attempted later. However, the patient has improved so markedly that the second stage has been postponed; she will be re-evaluated shortly.

The third patient, a boy 1⅔ years old, with drainage directly into the right atrium, was operated upon in an attempt to anastomose the left pulmonary vein to the left atrium. The patient died of blood loss due to complications arising from the small size of the structures.

Difficulties similar to our own in correcting this anomaly surgically, without the use of open heart surgery, have been experienced by others as well. Mustard and Dolan in 1957 reported 1 survival.[27] Burroughs and Kirklin[26] reported 9 attempts at correction without survival from the literature and one survival of their own.

Open heart surgery by means of the pump oxygenator was first used by Burroughs and Kirklin[26] in 1956 in 2 patients with 1 survival. In both these cases a side-to-side anastomosis between the divided common pulmonary vein trunk and the left atrium was carried out with accompanying closure of the patent foramen ovale. Open heart surgery by means of hypothermia has been used by Mustard and Dolan[27] in 9 patients with 4 survivals. In 2 of the 4 survivors, the vena cava was not completely occluded distal to the entrance of the pulmonary veins, much as in our second patient. Ehrenhaft et al.[28] recently reported the successful correction of one patient with hypothermia in which the ascending cava was

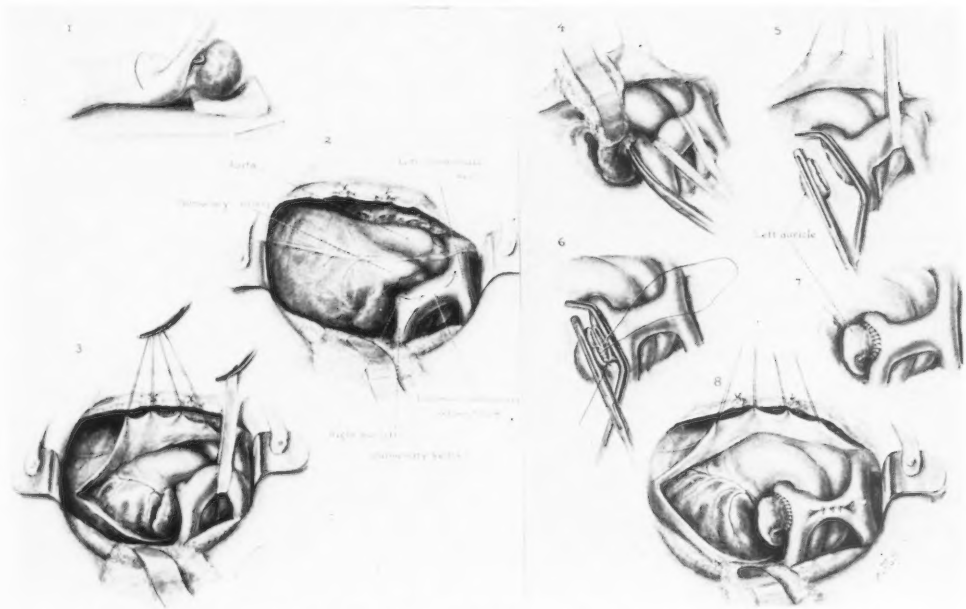

FIG. 9. The surgical technic employed in the successful firststage repair of complete transposition of the pulmonary veins into an ascending left superior cava.

divided and the atrial septal defect was closed.

Our very favorable experience with open heart surgery by means of the pump oxygenator in the correction of various intracardiac anomalies suggests that this method will without question be the procedure of choice for correction of total transposition of the pulmonary veins in the future. If the common pulmonary vein trunk enters the superior vena cava, direct anastomosis to the left atrium will be possible. If the entrance of the veins is into the coronary sinus or the right atrium proper, then by means of shifting the septum, the anomalous structures may be caused to drain into the left atrium.*

SUMMARY

The literature on complete transposition of the pulmonary veins is reviewed. Twenty patients studied by us are reviewed in detail. There was no correlation between the relative size of the interatrial communication and the age of death.

Frequent symptoms were easy fatigability, dyspnea, and recurrent respiratory infections. Examination commonly revealed mild cyanosis, congestive failure, and a characteristic triple or quadruple rhythm. Soft systolic and apical middiastolic murmurs were common; a medium-pitched presystolic murmur was present in one third.

Electrocardiograms demonstrated marked right ventricular hypertrophy with complete reversal of the R/S progression. Radiographic patterns usually could be correlated with the level at which the pulmonary veins emptied. Cardiac catheterization data revealed an interesting inverse relationship between right atrial pressure and systemic index.

Patients with drainage into the portal system formed a unique group. All were males, succumbed early, were more intensely cyanotic, and had marked hepatomegaly. X-rays revealed a normal-sized heart with intense pulmonary engorgement.

*Since this paper was written, 1 patient with total pulmonary venous transposition into the superior vena cava has been successfully operated on with the use of the pump oxygenator. The whole connection was severed after a side-to-side anastomosis between the left atrium and the pulmonary venous connection to the superior vena cava had been made.

Reported experiences with surgical correction are reviewed, and 3 of our operated cases are presented. Using closed technics, we have 1 survivor. Open heart surgery, with a pump oxygenator, is suggested as the optimal approach for these individuals.

Incomplete Transposition of the Pulmonary Veins

Definition

In incomplete transposition of the pulmonary veins, the major abnormality is the anomalous drainage of *part* of the pulmonary return into the right atrium or its tributaries. We have excluded from our series all cases with other major cardiovascular lesions, except a patent foramen ovale or a secundum-type atrial septal defect.

Incidence

The exact incidence of incomplete transposition of the pulmonary veins is difficult to estimate, since the anomaly may not be suspected clinically and, if the heart is dissected from the lungs in the initial stages of necropsy, anatomic diagnosis may be impossible. There have been well over 100 cases reported in the literature; and, based on careful studies, the incidence is probably 6 to 10 per 1000 routine autopsies.[4, 29, 30] Of the first 37 patients with secundum-type atrial septal defects operated upon by Gross and Watkins,[31] 9 had incomplete transposition of the pulmonary veins.

Embryology

Brown,[32] who first described the development of the pulmonary circulation from part of the presplanchnic plexus, also noted the central position of the opening of the common pulmonary vein in the dorsal wall of the sinus venosus, and described the shift of the pulmonary veins to the left with formation of the atrial septum. Davies and MacConaill[33] proposed that a portion of the right wall of the common pulmonary vein actually initiated the formation of the atrial septum, by invaginating the dorsal wall of the sinus venosus. Anomalies of the pulmonary venous return could logically be attributed either to a failure of some of the pulmonary veins to migrate to the left of the developing atrial septum, or to defects of septation, perhaps originating in abnormal invagination from the common pulmonary vein; it is interesting to note in this respect the frequent coexistence of atrial septal defects with anomalies of the right pulmonary veins.

Anomalies of the left pulmonary veins are rarely associated with atrial septal defects and are presumably due to failure of those veins to connect with the common pulmonary vein, and subsequent persistence of their earlier connections with the branches of the cardinal veins.

Anatomic Considerations

Anomalies of the right pulmonary veins are at least twice as frequent as anomalies of the left. The anomalous right pulmonary veins drain most commonly into the superior vena cava or right atrium, and are frequently associated with an atrial septal defect. Anomalies of the left pulmonary veins are more apt to occur as an isolated abnormality, and usually drain into the left superior vena cava, left innominate vein, or coronary sinus. Only 2 cases have been reported of anomalous drainage of part of both lungs.[2]

The associated changes in the cardiovascular system at necropsy vary with the number of anomalous pulmonary veins and with the presence and size of an atrial septal defect. Although, as Brody originally pointed out, "incomplete drainage is not incompatible with long life"[2] the complacency of most subsequent reviewers toward this anomaly is not justified by the case reports in the literature.

Brody further qualified his prognostication with the statement that, of 25 patients in whom more than 75 per cent of the pulmonary flow returned normally to the left side, all but 2 lived to be adults. Brody reviewed 42 patients without other major cardiac abnormalities, excepting atrial septal defects, and the actual age at death varied greatly; however, at least 14 died before the age of 40 (table 4). It should be borne in mind that 40 years is the average life span of patients

with atrial septal defects, coarctation of the aorta, and patent ductus arteriosus.[7, 34, 35] Such prognostications, based on age at death of autopsied patients, have no clear validity, particularly when it is uncertain in a large number of Brody's cases whether there were associated septal defects, and whether the cause of death could reasonably be ascribed to the cardiovascular anomaly under discussion. Certainly, estimates of the volume of the shunt based on the number of anomalously draining veins, or even cross-sectional areas of the veins,[30] are inaccurate, since they fail to account for differential pressure gradients.

In brief, there is no logical basis for the assumption that incomplete transposition of the pulmonary veins is a benign condition, and the significance of the anomaly must be assessed separately in each individual.

Physiology

Incomplete transposition of the pulmonary veins usually produces a small to moderate sized left-to-right shunt when not accompanied by an atrial septal defect or other major cardiac abnormality. Right-to-left shunting on the other hand, causing arterial unsaturation, is impossible when the septa are intact, thus, placing this anomaly in a unique position in the group of left-to-right shunts.

Because of the frequent association of anomalies of pulmonary return with atrial septal defects, detailed reports of cardiac catheterization in the isolated anomaly are infrequent, and often proof is lacking that the atrial septum is intact. Jonsson[8] reported 3 proved cases with intact atrial septum, and the ratios of pulmonary to systemic blood flow were 1.9, 1.8, and 1.6. Snellen and Huber's case[23] demonstrated a ratio of 1.4. Friedlich et al.[36] reported a patient who had a pulmonary blood flow of 8.3 L. per minute per M.^{2} which is more than twice the normal systemic output, although no calculation of actual systemic flow was presented. Knutson's[37] 2 patients had pulmonary flows 1.8 and 2.2 times as large as systemic. An atrial septal defect could not be ruled out in any of the last 4 patients. However, these figures

TABLE 4.—*Age at Death of 42 Cases of Incomplete Transposition of the Pulmonary Veins*[2]

Years	Number of deaths
Less than 1	6
1–20	2
21–40	6
41–50	5
51+	9
"Adults"	14

are predominantly in the range of "large" shunts,[34] and, in the presence of marked cardiomegaly, congestive failure, or marked limitation, these patients would be candidates for operative repair. Interestingly, when pressures in the right heart were reported, they were normal in 7 of 8 cases.[8, 23, 36-38]

As was emphasized in the anatomic discussion, the pulmonary blood flow cannot be accurately estimated by the number of anomalously draining veins alone. Since right atrial pressure normally is 4 to 5 mm. Hg less than the left, the pulmonary artery furnishes a pressure head effectively 5 mm. greater for flow through an anomalous vein than through a normally draining vein of comparable cross-sectional area. If the patient has 4 normally draining veins, the left-to-right shunt through one anomalous vein of comparable size would be 29 per cent of the total pulmonary blood flow, and the total pulmonary blood flow would be 1.4 times greater than systemic.* Similarly, if 2 and 3 veins drained anomalously with normal pressures throughout both systems, the total pulmonary blood flow would be respectively,

*With 4 normal and one transposed pulmonary vein, assuming equal cross sectional areas for all 5 veins, and normal mean pressures in pulmonary artery, left atrium, and right atrium (viz., 15, 7, and 2 mm. Hg, respectively), then:

$$Qp = Qs + Qapv$$

$$Qapv = \frac{Qs}{4} \times \frac{15\text{-}2}{15\text{-}7}$$

$$Qp = 1.4 \times Qs$$

$$Qapv = .29\ Qp$$

Where Qp = total pulmonary flow
Qs = systemic flow
$Qapv$ = flow through anomalous pulmonary vein(s).

2.1 and 3.4. With transposition of 3 pulmonary veins, even if the right and left atrial pressures were identical, the total pulmonary flow would be 2.5 times systemic. These calculated figures are of the same order of magnitude as those available from the literature. It would, therefore, seem unwarranted a priori to predict a normal life span for patients with this condition.

The importance of 1 or 2 transposed pulmonary veins may be greatly magnified in patients with pulmonary disease, particularly where resection or collapse therapy is contemplated. Removal or collapse of a normally draining lobe would reduce the useful pulmonary return proportionally, and in situations in which 1 entire lung is drained abnormally, resection of the other lung would create *complete* transposition of the pulmonary veins, and survival would depend upon a patent foramen ovale or septal defect. Consequently, any candidate for such procedures should be carefully evaluated, if there is even minimal cardiomegaly, engorged pulmonary vasculature, or shadows suspicious of anomalous pulmonary veins.

Also, it should be borne in mind, that a lobe or lung with transposed veins is not necessarily functionless even though inefficient. It may exchange as much carbon dioxide and oxygen as the normally draining lung if the parenchyma is normal, since the concentrations of these gases are the same in both pulmonary arteries and in both sets of pulmonary veins. The anomalously drained lung may contribute 50 per cent or more to the total body gas exchange, which may be critical in some pulmonary diseases. In such patients, resection should be preceded by differential bronchospirometry.*

*Arvidsson[38] reported the results of bronchospirometry in a patient with drainage of all of the right lung into the inferior vena cava, and with apparently normal pulmonary function. The right lung, absorbed 138 ml. oxygen per minute, the left 212 ml., although the vital capacity of the 2 lungs was 600 and 720 ml. respectively. In this case, the left-to-right shunt would be only 40 per cent of the total pulmonary blood flow.

Presentation of Data

Eleven patients with incomplete transposition of the pulmonary veins have been observed by us in the past 6 years. Ten patients were studied by cardiac catheterization, and 9 of these underwent surgical repair. Four patients were autopsied; 1 of these had not been diagnosed by catheterization. Nine patients were found either at surgery or autopsy to have an associated atrial septal defect of the secundum type, and a tenth patient with a calculated pulmonary blood flow 4 times systemic is presumed to have an atrial defect.

Nine patients had anomalous drainage of 1 or more right pulmonary veins into the right atrium. Two of these patients had additional veins from the right upper and middle lobes draining into the superior vena cava. One patient had only 1 vein from the right upper lobe draining anomalously into the superior cava. In our series, there was no instance of 2 of the 3 right lobes draining anomalously, but either all the right lobes or only 1 drained anomalously. Four of 10 patients had single vein transposition, and these were all from the right upper lobe.

The 1 patient with transposition of the left pulmonary veins had only a small, patent foramen ovale; the 2 anomalous veins drained into the innominate vein and coronary sinus respectively. This patient died at 2 months of pneumonia, and had moderate dilatation and hypertrophy of the right heart. Catheterization was not performed.

The patients' ages ranged from 2 to 40 years, with an average of 15 years, which is in marked contrast to the ages of patients with complete transposition of the pulmonary veins. The sex distribution reflected the incidence in patients with atrial septal defects: 3 males and 7 females. (The patient with the isolated anomaly was a male.)

History

There was no family history of heart disease from any patient, and only 1 patient's gestational history was abnormal, with maternal rubella in the first trimester.

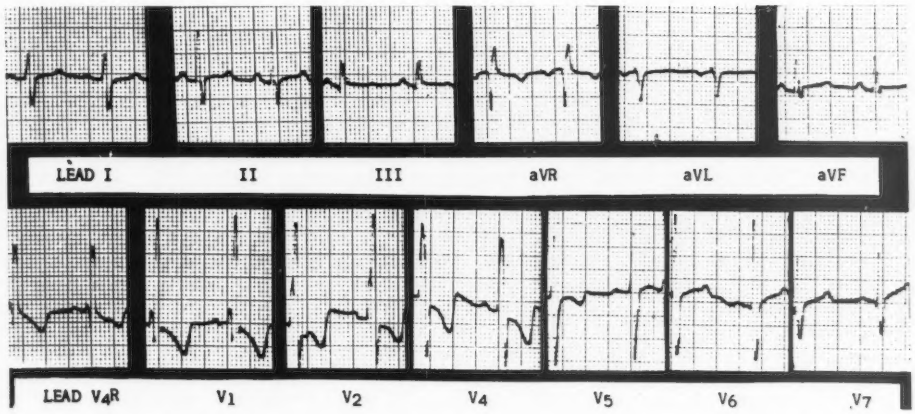

FIG. 10. Representative electrocardiogram of a patient with transposition of the right pulmonary veins, and an atrial septal defect, illustrating incomplete right bundle-branch block and right ventricular hypertrophy.

Dyspnea, fatigue, and frequent respiratory infections were the commonest complaints, occurring in 7 cases. Cyanosis was not noted by any parent. A history of edema was given in 2 instances. Two of the older patients have documented histories of paroxysmal atrial tachycardia, a frequent finding in older patients with atrial septal defects. No patient was completely asymptomatic.

Physical Findings

Our patients with incomplete transposition of the pulmonary veins presented a less striking physical profile than the individuals with the complete anomaly. Six of the patients were well developed and 5 were below the twenty-fifth percentile for height, although 3 of them were thin. None of them was cyanotic or had clubbed nails. Two patients, 8 and 9 years old respectively, were in congestive failure, with hepatomegaly and engorged veins. Precordial bulge was noted in 5 patients; the point of maximal impulse was at the lower left sternal border in all. Two patients had palpable thrill in the pulmonic area: in the first, a systolic thrill was associated with a gradient of 32 mm. Hg, across the pulmonic valve; in the second, a 20-year-old patient with pulmonary hypertension, an early diastolic thrill was demonstrated.

On auscultation, the first sound was increased in intensity in 8 patients, and normal in 3. The pulmonic sound was accentuated in 6, normal in 5, and audibly split in all 11. A third sound was detected in 4 individuals and a fourth, or atrial sound was present in only 2. Systolic murmurs at the upper left sternal border were present in all 10 patients with atrial septal defects, but not in the patient with the isolated venous anomaly. The systolic murmur was soft and blowing in character except in 4 instances. These 4 patients had a rough, systolic murmur that transmitted. During cardiac catheterization, a moderate pressure gradient across the pulmonic valve was recorded. Mid-diastolic murmurs at the apex or lower left sternal border, characteristic of large left-to-right shunts were found in 8 patients.[34] Three individuals had early, high-pitched diastolic murmurs at the pulmonic area; these patients were older (20, 22, and 40 years respectively), and 1 had severe pulmonary hypertension. Four patients had presystolic murmurs similar to those present in complete transposition of the pulmonary veins. This murmur, diamond-shaped, of medium to high frequency and synchronous with atrial systole, was accompanied by a fourth sound in 2 patients.

Electrocardiogram

The electrocardiogram of patients with

FIG. 11 *Top.* Representative radiogram in a patient with transposition of the right pulmonary veins into the right atrium and an atrial septal defect.

FIG. 12 *Bottom.* Radiogram of a patient with transposition of the left pulmonary veins and an intact septum.

incomplete transposition of the pulmonary veins reflects the increased volume of the right ventricle although these changes are less marked than in the patients with complete transposition of the pulmonary veins. Right axis deviation was present in 9 patients, normal electric axis in 2. All 11 patients had right ventricular hypertrophy, but only 5 patients, including the 1 with the isolated anomaly, had marked right ventricular hypertrophy, as suggested by complete reversal of the adult R/S progression, or large right ventricular potentials, or both. Incomplete right bundle-branch block was present in every instance; right ventricular intrinsicoid deflection was consistently prolonged, with an average of .06 second. Figure 10 shows a representative electrocardiogram.

The pattern of P pulmonale, so frequent in complete transposition of the pulmonary veins, was present in only 3 patients with the incomplete anomaly. Similarly, T-wave changes were found in only 4 patients, 2 of whom were on digitalis.

X-Rays

The radiographic profile of our patients with incomplete transposition of the pulmonary veins was completely nonspecific, although quite similar to that in patients with atrial septal defects. The specific pattern reported by Steinberg et al.[39] observed in patients with 1 or 2 right pulmonary veins draining into the inferior vena cava was not observed in our cases; in fact, there was no radiologic suggestion of the existence of anomalous pulmonary veins in any of our patients.

Cardiomegaly was present in all of our patients: it was slight in 4, moderate in 4, and marked in 3 patients (figs. 11 and 12). In every instance, the ventricular configuration was characteristically right-sided. Atrial enlargement was present in 9 patients, but not in the patient with intact atrial septum. The main pulmonary artery was abnormally prominent in all patients, with slight to moderate enlargement in 8 and marked enlargement in 3. Pulmonary vascular engorgement was present to a moderate degree in 8 of the 10 patients with atrial septal defects; 2 patients had marked engorgement. The patient with an intact septum had mild engorgement. "Hilar dance" was observed in 9 patients; it was not detected in the 2-month-old patient with an intact septum, nor in the youngest patient with an associated atrial septal defect. The aorta was judged to be smaller than average in 5 patients.

Angiocardiograms were not performed in any of our patients with incomplete transposition of the pulmonary veins.

It is interesting that the patient with an intact septum had moderate cardiomegaly,

TABLE 5.—*Cardiac Catheterization Data of Patients with Incomplete Transposition of the Pulmonary Veins, Associated with Atrial Septal Defect*

Patient number	1	2	3	4†	5	6	7	8	9†	10
Age	5½	8½	20	28	2	9	9½	16	22	40
Number of transposed veins	1	1	1	1	3	3	3	3	3	3
Rise in O_2 at right atrium (vol. %)	3.0	4.8	4.4	3.3	3.5	3.4	3.0	3.0	2.7	3.5
(% saturation)	19	31	24	18	23	20	19	15	15	19
Systemic artery (% saturation)	96	98	95	95	97	97	97	97	99	98
Pulmonic artery (% saturation)	85	93	89	93	93	93	92	92	88	90
Systemic index (L./min./M.²)	2.6	2.9	2.2	2.6	4.5	3.8	5.7	4.2	2.5	2.9
Pulmonic index (L./min./M.²)	6.7	17	6.5	11	19	15	13	13	6.2	8.9
Resistances ratio (Pul/Systemic)	1/30	1/65	1/5	1/32	1/58	1/24	1/12	1/11	1/12	1/9
Wedge pressure (mm. Hg)	—	13	10*	5	—	6	—	—	7	7*
Right atrial pressure (mm./Hg)	6	10	10	2	4	5	2	7	3	6
Vein entered with defect	+	0	0	+	+	0	+	+	+	0
Position of ASD	mid-post	low post	low post	high post	—	low post	high post	low post	high post	high post

* Actual left atrial pressure.
† Patient 4 was catheterized by Dr. D. S. Lukas at the New York Hospital, Patient 9 was catheterized at the Brooke Army Hospital, San Antonio.

and marked right ventricular hypertrophy on electrocardiogram with only 2 pulmonary veins draining anomalously. His death at 2 months was secondary to pneumonia, but these changes nevertheless suggest that the isolated transposition of even 2 pulmonary veins may be a moderately serious burden to the heart.

Cardiac Catheterization

Ten patients with incomplete transposition of the pulmonary veins were studied by cardiac catheterization because of symptoms and signs suggesting a large atrial septal defect. The 1 patient with an intact septum was not catheterized. Eight of the 10 patients were catheterized in our laboratory; 2 adults were catheterized elsewhere (table 5), although the remainder of their clinical examination and operative procedures were performed by us.

Arterial oxygen saturation in these patients showed no overlapping with those of the total anomaly; 95 per cent was the lowest saturation obtained and the average was 97 per cent.

The rise in oxygen saturation at the right atrial level varied from 15 to 31 per cent, with an average of 20 per cent. This also reflects the left-to-right shunt through the atrial septal defect, of course.

Cardiac output varied from 2.2 to 5.7 L. per minute per M.², with an average of 3.4, within normal limits for systemic index. Pulmonary flow ranged from 6.2 to 19 L. per minute per M.², with an average of 12. There was an average left-to-right shunt of 8.5 L. and no definite right-to-left shunt in any patient. These calculated flows are approximations, at best, because a true mixed venous sample is impossible to obtain.

Right atrial pressures in the incomplete anomaly varied less than in complete transposition of the pulmonary veins, ranging from 2 to 10 mm. Hg, with an average of 5. The interesting inverse relationship between left ventricular output and the right atrial pressure that was present in the complete anomaly, was also present in patients with incomplete transposition of the pulmonary veins (fig. 13). The pressure relationship between the right atrium and left atrium (or wedge pressure) was determined in 7 patients, and similar to the findings in large atrial septal defects,[25] the gradient between left and right atria averaged only 2 mm. Hg.

Four patients had gradients across the pulmonic valve of 10, 18, 28, and 32 mm. Hg. Although none of these patients was autopsied, it seems unlikely that anatomically detectable stenosis was present, since they had flows through the valve of 8, 9, 15, 13, and 19 L. per minute, respectively. It is probable

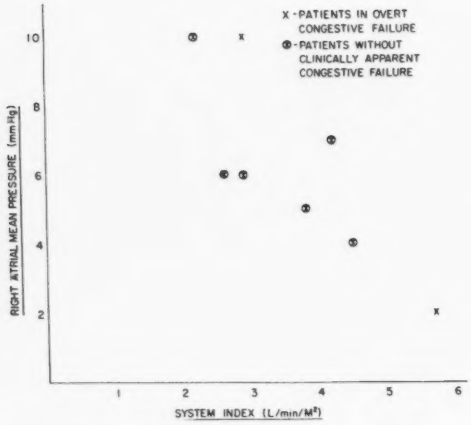

FIG. 13. Graph of the relationship of right atrial pressure to left ventricular output in patients with incomplete transposition of the pulmonary veins and atrial septal defect.

that, at normal flows, the gradient would be insignificant.

Pulmonary vascular resistance was abnormally increased in only 1 patient, a 20-year-old girl, whose calculated resistance was 328 dynes-second-cm.$^{-5}$, and a ratio of pulmonary to systemic resistance of 1 to 5. This patient died shortly after surgical repair, and was found to have moderately severe medial hypertrophy and intimal hyperplasia of the pulmonary arterioles. The other patients, including a 40-year-old woman, had essentially normal resistances. The average pulmonary vascular resistance in the entire group of catheterized patients is considerably less than normal, with a ratio of 1 to 25, pulmonary to systemic, consistent with the findings of patients with atrial septal defects without pulmonary vein anomalies.[34]

Although the possibility of incomplete transposition of pulmonary veins was considered prior to cardiac catheterization, it was not specifically diagnosed in any case. At the time of catheterization, however, an anomalous pulmonary vein was entered, from the superior vena cava in 2 cases, and the right atrium in 4. In the remaining 4 cases, the pulmonary vein anomaly was discovered at the time of operation. Even in those cases in which a pulmonary vein was apparently catheterized from the right atrium, the diagnosis of transposition of a pulmonary vein should be made with reservations, since it is quite possible to slip across into the left atrium through a high, posterior septal defect into a normally draining vein. Avoiding this error requires careful 3-dimensional checks on position and frequent sampling. Figure 14 illustrates the position of the cardiac catheter in anomalously draining veins, subsequently confirmed at operation.

Although, in some cases, dye-dilution curves may help in the diagnosis of co-existence of incomplete transposition of the pulmonary veins and an atrial septal defect, this technic is as limited as that of passing the catheter into the anomalous pulmonary veins. Due to the proximity of the normally connecting right pulmonary veins to the atrial septal defect, perferential shunting of venous return from the right lung may simulate the curves of anomalous venous connection from the right lung.[40] None of our patients had dye-dilution studies.

In view of our present surgical approach to atrial septal defects, the presence of anomalous pulmonary veins is of no major consequence either in selecting candidates for surgery, or in selecting the external approach. In cases of the isolated anomaly, with an intact atrial septum, more exact anatomic information would be crucial, in which case, selective angiocardiography would be of great assistance.

Surgery

Seven patients with incomplete transposition of the pulmonary veins have been operated upon at the Children's Medical Center,[31] by a method similar to that initially described by Neptune, Bailey, and Goldberg,[41] in which pulmonary veins connecting to the right atrium, in association with a posterior defect, are rechanneled by atrioseptopexy. This technic takes advantage of the fact that most, if not all, cases of incomplete transposition of the pulmonary veins to the right atrium are associated with posterior defects, which are

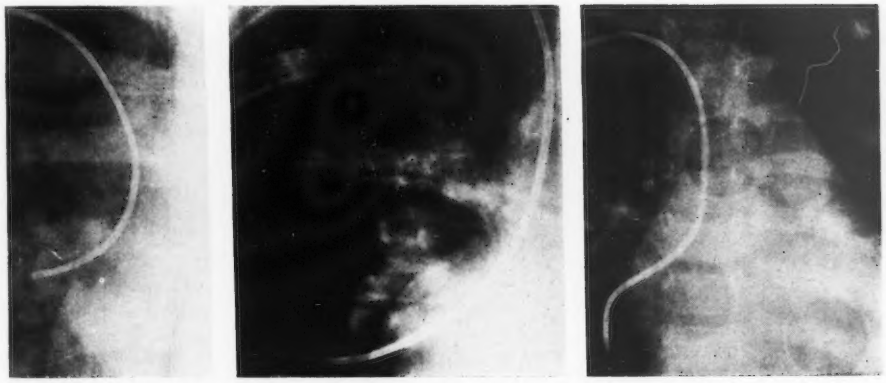

FIG. 14. Radiogram, illustrating the cardiac catheter in pulmonary veins entered from the right superior vena cava and right atrium.

ideally suited for closure by invagination of the right atrial wall, thereby enlarging the atrium to include the entry of the anomalously draining veins, but excluding the systemic return from the superior and inferior venae cavae and coronary sinus.

An eighth patient, not included in the clinical part of this discussion, was operated upon recently by means of open heart surgery through a pump oxygenator. This subject had a posterior defect in the atrial septum, 1.5 cm. wide and 2 cm. long. Two right pulmonary veins came into the right atrium. Repair was accomplished in such a way as to bring the anterior edge of the septal defect over against the back wall of the atrium, to the right of the anomalous veins. In this way the defect was closed and all the pulmonary veins were directed into the left atrium.

Various surgical technics have been proposed to correct the drainage of veins into the right superior vena cava. Since the external approach for atrioseptopexy is through the right chest, actual transplantation of the veins into the left atrium is difficult, if not impossible, without open heart surgery. Resection of a lobe or entire lung should be regarded as a last resort, and should be preceded by careful studies of cardiac and pulmonary functions, including differential bronchospirometry. Two of our patients with atrial septal defects and partial transposition of the pulmonary veins had this anatomic situation. Only the atrial defect was repaired in these children. Ehrenhaft et al.[28] reported 4 patients operated upon with hypothermia, with closure of atrial defects. They transplanted the superior vena cava, and in 2 of these patients, they utilized an arterial graft.

Ligation of the anomalous pulmonary veins seems less than completely satisfactory. Ligation of all the veins from 1 lung is frequently fatal.[43] Tying off a single vein, although well tolerated in 1 of our patients, may cause congestion of the involved lobe. Also, the anastomoses connect with the bronchial veins, or with the parietal veins, *both* of which ultimately drain into the right atrium, since there are no important translobar anastomoses with normally draining pulmonary veins.

Moderate, or even severe pulmonary hypertension in a patient with an intact atrial septum, and incomplete transposition, would not be a contraindication to surgery, since repair would diminish the right ventricular work and increase the left-sided return. This is in contradistinction to patients with atrial septal defect and severe pulmonary vascular obstruction, in whom a right-to-left shunt through the septal defect may allow more adequate systemic output as this disease progresses.

Of the 10 patients with atrial septal defect and transposed pulmonary veins to the present time, 8 had successful closures of the septal defect and correction of all the anomalous

drainage. In the 2 with superior vena cava drainage, only the atrial septal defect was repaired. There were 2 deaths: 1 secondary to infarction of the right atrial wall including the pacemaker, and 1 in whom a plastic button was used in the early stages of developing operative approaches for repair of atrial septal defects. The results obtained in the surviving patients are considered excellent.

Summary

The seriousness of incomplete transposition of the pulmonary veins has probably been underestimated in the past.

Data on 11 patients is presented, including 10 with associated atrial septal defects. Common symptoms were dyspnea, fatigability, and frequent respiratory infections. Examination revealed no cyanosis, widely split second sound, soft systolic murmur and middiastolic murmur at the apex. One third demonstrated a presystolic murmur of medium pitch. The electrocardiographic and radiographic features were characteristic of atrial septal defects. There were no specific vascular shadows in any of our patients. Catheterization data were also characteristic of atrial septal defects. There was an inverse relationship between the right atrial pressure and systemic index. Anomalous pulmonary veins were entered during the right heart catheterization in 6 of the 10 patients catheterized.

Seven patients have had atrioseptopexy to close the septal defect and to direct the blood from the anomalously draining veins into the newly enlarged left atrium. An eighth patient had repair and shift of the atrial septum by means of open heart surgery through a pump oxygenator. This approach will probably prove optimal for future operations.

Acknowledgment

The cardiac catheterizations reported in this paper were performed by Drs. Walter T. Goodale and Abraham M. Rudolph, in the Cardiovascular Laboratory of the Children's Medical Center, Boston, with the exception of 2 patients with incomplete transposition of the pulmonary veins catheterized by Dr. D. S. Lukas, at the New York Hospital, and 1 patient at the Brooke Army Hospital, respectively. Permission to include these data is gratefully acknowledged. We also wish to thank Dr. M. W. Wittenborg, who reviewed the radiographic findings, and Dr. J. B. Craig, for reviewing the anatomic findings.

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ABSTRACTS

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PHARMACOLOGY

Young, I. M.: Some Observations on the Mechanism of Adrenaline Hyperpnoea. J. Physiol. 137: 374 (Aug.), 1957.

Hyperpnea is frequently produced by intravenous administration of epinephrine in man. The increased respiration is an increase in tidal volume with little alteration in respiratory rate in the anesthetized animal and in conscious man. The mechanism for this is unknown. An investigation was undertaken to discover the mode of action of epinephrine in stimulating respiration in the anesthetized animal. Records of respiratory rate and minute volume were obtained and arterial blood pressures were measured. A continuous infusion of epinephrine was given. The blood supply to the medulla was isolated by ligation of the vertebral arteries. The infusion was given directly into these. In another set of experiments the injection of epinephrine and norepinephrine was given into the carotid and aortic vessels after the common carotids and the aorta had been denervated by stripping the plexuses from these vessels. Maximum contractions of gastrocnemius muscle were measured simultaneously with respiration. Infusions were given to animals in whom the adrenal glands had been removed, in whom ligation of blood supply to the kidney had been performed, and in whom removal of the entire gut had been effected. In the intact animal hyperpnea was produced with infusions of 0.12 to 0.5 micrograms of epinephrine. There was increase in minute volume caused by a rise in tidal volume. The respiratory responses were accompanied by a short-lasting rise of arterial blood pressure. Injection into the vertebral artery to stimulate the respiratory center in the medulla had no effect on respiration or minute volume. Blood pressure changes did occur. Infusion of epinephrine into the carotids or aorta previously stripped of their plexuses caused the same respiratory response as that in the controlled animals infused intravenously. Epinephrine had no action directly on the skeletal muscle even though there were marked changes in stimulation of respiration tested at the same time. The experiments showed that the respiratory response to intravenously administered epinephrine was independent of the vagus, carotid and aortic nerve plexeses, and had no direct effect on the medullary center. The action of epinephrine in producing this hyperpnea was unproved by these experiments.

HARVEY

Moyer, J. H., Seibert, R. A., and Handley, C. A.: Chromatography Studies of the Excretion Products after Meralluride Administration in Normal Subjects and Cardiac Patients. Circulation Research 5: 493 (Sept.), 1957.

One concept for the diuretic action of organomercurial compounds is that they release inorganic mercury in the body, which is thought to inhibit the renal tubular enzymes responsible for sodium and chloride reabsorption. Separation of the urinary excretory products of meralluride (Mercuhydrin) by adsorption chromatography does not favor this theory. Practically all of the mercury is excreted in a form closely resembling the administered meralluride. The amount of mercury excreted as degradation products is insufficient to produce diuresis. It is concluded that the diuretic action of meralluride depends on the specific organic mercurial molecule.

AVIADO

PHYSICAL SIGNS

tuckey, D.: Palmar Pulsation: A Physical Sign of Patent Ductus Arteriosus in Infancy. M. J. Australia **2:** 681 (Nov. 9), 1957.

Pulsation of the superficial palmar arch over ie metacarpal heads was palpable in 21 of 22 ifants and children having a patent ductus rteriosus. This sign was present in only 14 of 0 age-matched children having other types of ongenital heart disease and in 18 of 84 normal hildren. The pulsation appears with increasing requency in older normal individuals, usually eing present in adults. It is nearly always resent when the pulse pressure by the cuff ethod is over 50 mm. Hg; and it can occur in otherwise normal children who are febrile, anemic, or in a hot environment. When the latter conditions are excluded, the detection of palmar pulsation is a useful confirmatory sign of patent ductus arteriosus, especially in infancy; its absence makes it unlikely that a sizable ductus exists.

ROGERS

Reinhold, J., and Rudhe, U.: Relation of the First and Second Heart Sounds to Events in the Cardiac Cycle. Brit. Heart J. **19:** 473 (Oct.), 1957.

The authors investigated the nature of the first and second heart sounds by relating their components to events in the cardiac cycle by timing with synchronous border electrokymograms. Aortic valve opening and closure were denoted respectively by the beginning of the rise of the aortic electrokymogram and its dicrotic notch. The pulmonary electrokymogram was similarly used for pulmonary valve opening and closure. mitral valve closure was denoted by the onset of the isometric ventricular phase as visualized on the left atrial electrokymogram. Tricuspid valve closure was regarded as synchronous with the onset of a sharp inflection preceding isometric right ventricular contraction as seen in the right atrial electrokymogram. The opening of these valves was regarded as synchronous with the sharp fall in the curve as rapid ventricular filling begins. The first sound has 4 components. The first occurs before isometric ventricular contraction; the second as the first major component with left ventricular isometric contraction and mitral valve closure; the third as the second major component with right ventricular isometric contraction and tricuspid valve closure and the fourth as the final component when the aortic and pulmonary valves open. The second sound has 2 major components, the first precedes the dicrotic notch on the aortic electrokymogram and is due to aortic valve closure and the second follows it but precedes that of the pulmonary electrokymogram and is due to pulmonary valve closure. Low-frequency terminal sounds were related by atrial electrokymograms to opening of the tricuspid and mitral valves. The tricuspid valve commonly opens first. These asynchronous movements of the right and left cardiac valves account for common splitting of the first and second sounds in the normal patient.

SOLOFF

PHYSIOLOGY

Lee, J. S., and Visscher, M. B.: Microscopic Studies of Skin Blood Vessels in Relation to Sympathetic Nerve Stimulation. Am. J. Physiol. **190:** 37 (July), 1957.

Stimulation of homolateral sympathetic trunks that supply the blood vessels of the skin of the leg was observed to produce a rise in the pressure of venules and small veins. At the same time the diameter of the vessels under observation was decreased. Following the termination of stimulation the veins and venules dilated even though the diameter of arterioles remained small. It was demonstrated that under the conditions of these experiments the pressure in venules may be elevated by sympathetic stimulation even though the arterioles, which supply the capillary bed that these veins drain, are contracted and thus reduce inflow into those capillaries.

OPPENHEIMER

Walker, S. M.: Fixed Coupling and Short P-R Interval Induced in the Dog by Stimulation of the Sympathetic Nerve System. Am. J. Physiol. **190:** 41 (July), 1957.

Strong stimulation of the sympathetic nervous system was produced by injection of a phosphate solution into the cisterna magna. The criteria of sympathetic stimulation were hypertension, tachycardia, and cardiac arrhythmias. If the vagi were cut, the observed results of phosphate injection were a few ectopic ventricular beats associated with ventricular tachycardia and bigeminy. Most often a normal beat of sinus origin was coupled with an abnormal ventricular beat. The latter was associated with a short P-R interval and prolonged duration of the QRS complex. Stimulation of the vagus inhibited the sinus impulse. However, the interval between the coupled beats was unchanged. The bigeminy depended upon fixed coupling of the ectopic ventricular impulse with the preceding beat of the pair.

OPPENHEIMER

Daly, I. B., and Daly, M. B.: Observations on the Changes in Resistance of the Pulmonary Vascular Bed in Response to Stimulation of the Carotid Sinus Baroreceptors in the Dog. J. Physiol. **137**: 427 (Aug. 6), 1957.

Experiments are presented in the dog anesthetized with chloralose to study the effect of the baroreceptors upon the control of pulmonary vascular resistance. The apical and cardiac lobes of the left lung were perfused with the bronchial circulation intact, but under a constant pressure to avoid any produced reflex responses on the pulmonary vascular bed with changes in systemic venous pressure. Systemic blood pressure and carotid sinus perfusion pressure as well as pulmonary arterial perfusion pressure, left atrial pressure, and right pulmonary arterial pressure were measured. The lungs were ventilated and mechanically the phrenic and recurrent laryngeal nerves were ablated. When the mean pressure in the carotid sinuses was increased, bradycardia, fall in systemic arterial pressure, and fall in pulmonary arterial pressure occurred. The pulmonary arterial perfusion pressure increased. Denervation of the carotid sinuses abolished this effect. After this was demonstrated in the preparation the lung was denervated by extirpation of the sympathetic nerves. A cervical vago-sympathectomy was performed. Repetition of the experiments produced identical results. It was thought that the observed change in the pulmonary vascular resistance was a passive alteration brought about by a redistribution of blood between bronchial and pulmonary vascular systems that accompanied the fall in systemic blood pressure when the carotid baroreceptors were stimulated.

HARVEY

Daly, I. B., and Daly, M. B.: The Effects of Stimulation of the Carotid Body Chemoreceptors on Pulmonary Vascular Resistance in the Dog. J. Physiol. **137**: 436 (Aug. 6), 1957.

Studies were performed to test the effects of stimulation of the carotid body chemoreceptors on pulmonary vascular resistance in the dog. It was found that stimulation of the chemoreceptors by perfusing first with venous blood and then with arterial blood caused a decrease in the pulmonary vascular resistance, for there was a measured reduction in the pressure gradient across the pulmonary vascular bed with constant blood flow. This response was independent of left atrial pressure and was not controlled by sympathetic innervation, for it remained after the destruction of the sympathetic nerves to the lungs. This response was abolished by cervical vagosympathectomy, or by sectioning of the carotid sinus nerves. It was concluded that the carotid chemoreceptor stimulation caused a reflex decrease in pulmonary vascular resistance that had as its pathway vagocholinergic fibers.

HARVEY

Agostoni, E., Chinnock, J. E., and Daly, M. B.: The Effects of Stimulation of the Carotid Sinus Baroreceptors Upon the Pulmonary Arterial Blood Pressure in the Cat. J. Physiol. **137**: 447 (Aug. 6), 1957.

In the dog, stimulation of the carotid baroreceptors results in a reflex fall in pulmonary arterial pressure. In the cat, on the other hand, other investigators have found that stimulation of the baroreceptors in the carotid artery has no effect on the pulmonary arterial pressure, despite considerable changes in systemic blood pressure. The authors investigated these effects on the pulmonary arterial pressure in the cat and found that stimulation of the baroreceptors in the carotid sinus caused changes in pulmonary arterial pressure. Cats were anesthetized with chloralose and artificially ventilated. The aortic nerves were isolated in the neck and appropriate means taken to stimulate them. The carotid sinuses were isolated from the circulation by ligation of all branches of the common carotid artery and these were then perfused with heparinized cat blood. The pulmonary arterial pressure and the left atrial pressure, the right atrial pressure, and systemic blood pressure were recorded by cannulation of the appropriate system. When the common carotid arteries were occluded bilaterally the pulmonary arterial pressure rose. This was accompanied by a rise in systemic blood pressure. Division of one or another of the carotid sinus nerves caused a rise in pulmonary arterial pressure. This was accompanied by rises in systemic blood pressure and acceleration of the heart. Stimulation of the carotid sinus nerves caused a bradycardia, a fall in systemic blood pressure and a fall in pulmonary arterial pressure. Stimulation of the aortic nerve caused the same effect. Raising the mean carotid sinus pressure resulted in a fall in systemic blood pressure, bradycardia, and fall in pulmonary arterial pressure. Denervation of the lung had no effect upon these reflexes.

HARVEY

Allen, F. M.: Infusion Treatment of Shock. Alkali and Acid in Shock Treatment. Arch. Surg. **75**: 210 (Aug.), 1957.

The efficacy of various types of alkali and acid in the therapy of experimental shock was explored. Both tourniquet and hemorrhagic shock were produced. Serial measurements were made of the hematocrit, protein, carbon dioxide volumes per cent, blood pressure, urine output, hindquar-

ter volume, body weight, fluid intake, and sodium chloride of plasma and urine. Survivals of 36 to 45 hours were obtained in animals with 5-hour tourniquet shock treated with isotonic saline. Neither plasma nor dextran produced as good results. When animals with 5-hour tourniquet shock were treated with Hartmann's solution intravenously and a solution of 3.5 Gm. of sodium chloride and 2.5 Gm. of sodium citrate per liter by stomach tube, the survival time was reduced to 21 to 28 hours. Dogs in similar shock treated with sodium lactate, sodium bicarbonate, and sodium citrate also had shortened survival times. "In general, death is hastened by increasing the quantity of any alkali; and particularly by any plan of holding the plasma bicarbonate up to the supposedly normal concentration." In another group of dogs successive bleedings to induce hyperpnea and consequent respiratory "acidosis," followed by successive bicarbonate injections to raise the plasma bicarbonate toward the accepted normal level resulted in death due to alkalosis, with normal or subnormal plasma bicarbonate concentrations. Dogs with 5-hour tourniquet shock received hydrochloric acid in saline intraveneously and ammonium chloride along with acid by mouth and survived the shock. The animals also survived when treated with acid entirely by vein or entirely by stomach except that recovery was slower by the single route. Delay in treatment of 1 to 2 hours still allowed for recovery but longer delays resulted in unusually long survival times but failure to recover. At autopsy, the fluid of the edematous legs and lungs was found to be swarming with bacteria indicating that the deaths were due to septicemia. In dogs subjected to a standardized procedure of bleeding to induce severe hemorrhagic shock, it was determined that no amount of saline could save these animals. In dogs with shock induced in this manner and treated with moderate amounts of intravenous hydrochloric acid in saline and 0.5 Gm. of ammonium chloride by stomach at the eighth hour, survival occurred. The plasma bicarbonate showed the usual fall at the end of bleeding but after 5 hours of acid injection it had risen in correspondence with the dogs' general improvement indicating a physiologic control rather than a passive store of sodium. The author views this work as a "rehabilitation of the chlorine ion, after the exclusive attention heretofore given the sodium ion."

BROTHERS

Brotmacher, L.: Evaluation of Derivation of Cardiac Output from Blood Pressure Measurements. Circulation Research **5**: 589 (Nov.), 1957.

The cardiac outputs measured by application of the Fick principle have been compared in 107 subjects with values calculated from the blood pressure, using various empirical formulas recently proposed by Hamilton, Remington, Starr and their respective associates. The best agreement was obtained with a formula suggested by Remington, which made allowance for the diminishing distensibility of the arterial system with increased pressure. The results obtained are considered too inaccurate to justify use of the method in measurement of output. The random nature of the discrepancies suggests that the results cannot be improved by modification of the existing formulas.

AVIADO

Holmes, R. L.: Cholinesterase Activity in the Atrial Wall of the Dog and Cat Heart. J. Physiol. **137**: 421 (Aug. 6), 1957.

This study demonstrates cholinesterase activity in the nervous elements in the atrial wall. Dog and cat hearts were obtained immediately after sacrifice, the hearts were fixed immediately, and complete endocardial layers were dissected free. Sections of the endocardium were laid out on slides and then soaked in substrate mixtures to localize by the histochemical technics of Koelle the tissue containing cholinesterase. Widespread cholinesterase activity was found in muscle of the atrial wall. The areas in the endocardial tissue that were terminal zones of nerve fibers showed strong cholinesterase activity. These thick fibers and end formations were found particularly in the junctional regions of the atria. None was found in the atrial appendage. The findings were essentially the same in the material from both dog and cat. By histochemical technics the enzyme was identified as predominantly the pseudo or nonspecific type.

HARVEY

Barcroft, H., Basnayake, V., Celander, O., Cobbold, A. F., Cunningham, D. J. C., Jukes, M. G. M., and Young, I. M.: The Effect of Carbon Dioxide on the Respiratory Response to Noradrenaline in Man. J. Physiol. **137**: 365 (Aug. 6), 1957.

It is known that an infusion of either epinephrine or norepinephrine causes a transient stimulation of respiration accompanied by reduction in the alveolar carbon dioxide pressure (pCO_2). To test whether the decline in pCO_2 may be due to hypoxia, the effects of infusions of norepinephrine were studied in human volunteers during the breathing of air containing 2 to 5 per cent CO_2, to maintain alveolar pCO_2 constant. Norepinephrine was used because it gave no subjective

symptoms. Carefully controlled studies were performed on human subjects. Psychogenic effects were minimized. Subjects breathed a mixture of air and CO_2 for 15 minutes and the respiratory minute volume and tidal pCO_2 were determined during the control period. Then an infusion of norepinephrine, 10 micrograms per minute, was given, and alveolar air samples were collected during this 15-minute period. A 15-minute recovery period ensued. The gas analyses were carried out by standard technics. Five experienced subjects were tested on 3 separate occasions. Most of the subjects had mild headache throughout the experiment, particularly when they breathed the inspired air containing 5 per cent CO_2. The respiratory rate was unaffected in 2 subjects, and in the other 3 there was a small maintained increase, particularly when breathing the 5 per cent CO_2 mixture. Alveolar pCO_2 showed a very small decrease in all subjects. This experiment showed that the continuous infusion of norepinephrine in subjects breathing air to which CO_2 was added converts the transitory increase in stimulation to breathing into a sustained one. No information was obtained from these experiments on whether the norepinephrine stimulated the respiratory center directly or reflexly in response to some peripheral action.

HARVEY

Kennamer, R., Miles, E., and Prinzmetal, M.: Studies on Lewis' Auricular Flutter of Post-Electrical Stimulatory Origin. Clin. Sc. **16:** 451 (Aug.), 1957.

Atrial flutter was readily produced by electric stimulation in dogs under morphine-paraldehyde-ether anesthesia without interposing an artificial crush barrier. When the stimulus was applied midway between 2 electrodes, the impulse arrived simultaneously at the recording electrodes. This is not consistent with a circus movement. Atrial flutter was produced from multiple sites in both atria and the time of arrival of the impulse at multiple exploring electrodes was determined. Depolarization occurred consistent with an ectopic focus rather than with a circus movement. Excitation was recorded simultaneously at multiple sites of the contralateral atrium. High-speed cinematographs disclosed that the atria contracted about the site of the stimulating electrode and radiated outward in all directions. There was no evidence of a narrow mother pathway and daughter waves.

KURLAND

Bolt, W., Valentin, H., and Tietz, N.: Pulmonary Artery Pressure, Heart Output and Respiration in Acute Respiratory Hypoxia Corresponding to Altitudes up to 4,000 and 5,000 Meters in Elderly Persons. Arch. Kreislaufforsch. **27:** 19 (Sept.), 1957.

In 9 persons 56 to 82 years old, respiration of air with progressively decreasing oxygen content up to a simulated altitude of 4,000 meters caused no appreciable change in oxygen uptake, type of respiration, or the heart rate. The oxygen content in arterial blood decreased 23 per cent; that in venous blood decreased 10 per cent; the decreased arteriovenous oxygen gradient corresponded to a 73 per cent increase in the heart output. In contrast to younger persons, this increase was not accompanied by an increase in the pulmonary arterial pressure, which usually decreased parallel to the systemic arterial pressure. This behavior may explain the clinical observation that elderly persons seem to be especially resistant to hypoxia at high altitudes and during operations.

LEPESCHKIN

Marshall, L. H., and Hanna, C. H.: Circulatory Reaction of Tolerant and Nontolerant Dogs to Polyvinylpyrrolidone and of Rats to Dextran. Am. J. Physiol. **189:** 209 (April), 1957.

Rapid intravenous injection of 350 mg. of polyvinylpyrrolidone (PVP) per kilogram produces hypotension, erythema, pruritus, and edema in dogs. These reactions became less severe or absent after pretreatment with the colloid. Similar observations were made with dextran in rats. Both colloids produce hypotension and increased capillary permeability. Dialyzed PVP did not produce a fall in blood pressure in dogs which were relatively tolerant.

OPPENHEIMER

Gerst, P. H., Taylor, C., and Peterson, L. H.: Indicator Recirculation as a Limiting Factor of Indicator Dilution Techniques. Am. J. Physiol. **189:** 191 (April), 1957.

Injections of dye into the root of the aorta were rapidly cleared from aortic and femoral sampling sites. In this case it was easy to detect recirculation from the time-concentration curves. When blood pressure is normal the onset of recirculation can be adequately approximated by the Hamilton semilogarithmic extrapolation procedure for short pulmonary artery injections. Hypotension makes this procedure less accurate. The Hamilton procedure will not detect recirculation from peripheral venous sites of injection.

OPPENHEIMER

Rose, J. C., and Freis, E. D.: Alterations in Systemic Vascular Volume of the Dog in Response to Hexamethonium and Norepinephrine. Am. J. Physiol. **191:** 283 (Nov.), 1957.

A diaphragm pump of controlled constant output was substituted for the left ventricle in dogs. Left atrial blood was conducted to a reservoir,

from which it was pumped into the thoracic aorta. Left ventricular by-pass was complete. Alterations in total vascular volume were continually monitored by observation of the pump reservoir level. Sympathetic blockade (hexamethonium) increased total vascular volume (mean 15 per cent). This resulted in decreased venous return and decreased right ventricular output. Norepinephrine constricted the total vasculature and decreased vascular volume (mean 12 per cent). This resulted in increased venous return and cardiac output. These experiments demonstrated the complex integrated responses of the total circulation to sympathetic vasomotor activity. The role of the sympathetic nervous system not only in the regulation of arteriolar tone and cardiac activity but also in adjusting total vascular volume and venous return was emphasized. Venous return, and hence cardiac output alterations accompanying systemic vasomotor activity, can only be detected by continuous methods of flow measurement.

WENDKOS

Randall, W. C., McNally, H., Cowan, J., Caliguiri, L., and Rohse, W. G.: Functional Analysis of the Cardioaugmentor and Cardioaccelerator Pathways in the Dog. Am. J. Physiol. **191**: 213 (Nov.), 1957.

The direct, electric stimulation of the thoracic anterior roots, the communicating rami, and the upper thoracic sympathetic trunk in the dog reveals the preganglionic pathways followed by the cardiac accelerator and augmentor nerves. These nerve fibers are generally intermingled in each of the above pathways, but accelerator fibers are much more prominent on the right, whereas augmentor fibers predominate on the left. The most significant pathways are via the T_2 and T_3 anterior roots and communicating rami, but significant responses were elicited from the T_4 nerves and occasionally from the T_1 and T_5 nerves. Neither accelerator nor augmentor responses could be induced by stimulation of the C_8 nerve nor by excitation of nerves below T_5. It is concluded that preganglionic cardiomotor fibers enter the trunk between T_1 and T_5, course cephalad to the stellate ganglion where they may synapse or pass to the caudal cervical ganglion by way of the ansa subclavia. The stellate cardiac nerve furnishes a very important postganglionic augmentor and accelerator pathway, when it is present, but direct branches from the caudal cervical ganglia carry a majority of these fibers in most animals. Augmentor and accelerator fibers cannot be functionally separated at any point in their anatomic pathways from the spinal cord to the heart. Responses seem to be determined rather, by the site of nerve terminations in heart tissue.

WENDKOS

Hoffman, B. F., Kao, C. Y., and Suckling, E. E.: Refractoriness in Cardiac Muscle. Am. J. Physiol. **190**: 473 (Sept.), 1957.

A preparation consisting of a papillary muscle and attached bundle of Purkinje fibers has been employed to study refractoriness of single cardiac fibers of the dog heart. Transmembrane stimulation of single fibers and records of the transmembrane potential have been used to compare the stimulating efficacy of applied current pulses and normally propagated action potentials. The absolute and effective refractory period and full recovery time of the single cardiac fiber are outlined in a similar manner by both applied cathodal stimuli and the propagated action potential. Two factors, a local response and a change in the local action potential, have been shown to contribute to the latency of response to stimuli applied during the relative refractory period. These studies have also demonstrated a considerable safety factor in propagation in cardiac muscle.

WENDKOS

Covino, B. G., and Beavers, W. R.: Cardiovascular Response to Hypothermia: Effect of Cold Acclimatization. Am. J. Physiol. **191**: 153 (Oct.), 1957.

The cardiovascular response to hypothermia was studied in dogs that had been exposed continuously to subzero arctic temperatures for a period of 1 to 4 weeks. All dogs exposed in this fashion showed a significantly lower terminal rectal temperature than unexposed control dogs. In addition, the incidence of ventricular fibrillation was reduced in direct proportion to the exposure period. Acclimatization to cold appeared complete in dogs exposed for a period of 4 weeks. In this group of animals, the frequency of ventricular fibrillation was reduced to 9 per cent as compared to an incidence of 96 per cent in the control dogs. The process of acclimatization occurred with extreme rapidity. Dogs that were deemed fully acclimatized, became deacclimatized after 5 days in a warm environment. Both the frequency of ventricular fibrillation and the mean terminal rectal temperature of this group were the same as that in the control unexposed group.

WENDKOS

Holland, W. C.: Potassium Exchange in Atrial Fibrillation. Am. J. Physiol. **190**: 63 (July), 1957.

The test objects were isolated rabbit atria. These were made to fibrillate by electric stimulation while suspended in a low potassium bath that contained acetylcholine. Observations were made on the rate of potassium loss. Stimulation in a low potassium medium at a slow rate caused a

mean net loss of potassium of 3.81 mM./Kg. tissues/5 minutes. A high frequency caused only a small additional loss. Under these circumstances fibrillation did not persist after stimulation stopped. The rate of loss of potassium was doubled when acetylcholine was added. Now, increase in rate of stimulation had a greater effect and arrhythmias sometimes persisted after stimulation ceased. Quinidine partially or completely blocked these actions and persistent arrhythmias were never observed. Fibrillation could begin when the rate of net loss of potassium exceeded a critical value.

OPPENHEIMER

Michel, D., Nöcker, J. and Hartleb O.: On the Circulatory Action of Adenyl Phosphoric Acid Compounds. II. Communication. Effect of Adenosine Monophosphate on the Pulmonary Circulation. Ztschr. Kreislaufforsch. **46**: 717 (Sept.), 1957.

During cardiac catheterization 20 mg. of adenosine monophosphate (Phosaden) were injected into the pulmonary artery in 15 persons. In the majority of individuals this was followed by a decrease in the pulmonary and systemic arterial pressures and an increase in the oxygen saturation of arterial blood. Patients without mitral disease showed improvement of oxygen saturation with an increase in pulmonary pressure, while patients with mitral disease showed this improvement with a decrease in pulmonary pressure.

LEPESCHKIN

PULMONARY DISEASES

Knisely, W. H., Wallace, J. M., Mahaley, M. S., Jr., and Satterwhite, W. M., Jr.: Evidence, Including in Vivo Observations, Suggesting Mechanical Blockage Rather than Reflex Vasospasm as the Cause of Death in Pulmonary Embolization. Am. Heart J. **54**:483 (Oct.), 1957.

The current belief that pulmonary emboli can cause fatal reflex pulmonary vasospasm was investigated by direct in vivo microscopy of the lungs of rabbits and cats during embolization with 10 to 2,000 micron particles or air bubbles. In the majority of the experiments 50 to 150 micron glass beads were used. Killing amounts of these particles were found to be the same in awake, anesthetized, thoracotomized, medicated, and vagotomized rabbits. During the experiments the unembolized pulmonary arteries were not observed to decrease in diameter and the embolized arteries never decreased in diameter proximal to the plug and did so distally only when collateral flow into that segment was markedly reduced or stopped. On the basis of their observations the authors conclude that the best interpretation of the cause of death from these emboli is that they mechanically blocked the pulmonary vessels. No observation necessitated the invocation of reflex vasoconstriction for it explanation. The authors further pointed out in a critical discussion that the animal-experimental literature relevant to the hypothetical reflex, the original articles on the pharmacology of papaverine regarding its ability to cause a reduction in pulmonary vascular resistance, and the clinical and pathologic literature on human pulmonary embolism do not support the concept of pulmonary reflex vasoconstriction following pulmonary embolism but indicate instead that mechanical blockage is the cause of death in pulmonary embolization.

SAGALL

Schenk, W. G., Jr., Bahn, R. A., Cordell, A. R., and Stephens, J. G.: The Regional Hemodynamics of Experimental Acute Arteriovenous Fistulas. Surg., Gynec. & Obst. **105**:733 (Dec.), 1957.

Large side-to-side fistulas between the femoral artery and vein or between the common carotid artery and external jugular vein in dogs were studied soon after their production by means of an electromanometer and an electromagnetic flowmeter. After opening the fistula, the proximal femoral artery flow increased 12-fold while the principal pressure change was a narrowing of the pulse. The distal femoral artery pressure fell 10 to 65 mm. Hg, mean, and the flow in most instances became nil. The proximal femoral vein pressure remained low or negative while the flow increased 5-fold. The distal femoral vein pressure increased to 50 to 100 mm. Hg, mean, and flow occurred away from the fistula at a rate usually much slower than that in the proximal vein. Similar changes occurred in the neck vessels proximal to the fistula. However, considerable flow occurred from the distal carotid artery into the fistula. In the distal jugular vein there was a sizable increase in flow and some increase in pressure, these functions differing in magnitude from those of the femoral vein probably owing to the presence of valves in the latter. Pressure studies alone are of little value in measuring either the magnitude or the direction of blood flow about fistulas.

ROGERS

Desbaillets, P., Reymond, C., and Rivier, J. L.: Demonstration During Cardiac Catheterization of an Anastomosis of the Pulmonary Artery with a Bronchial Vein. Cardiologia **31**:30 (Oct.), 1957.

In a patient with rheumatic mitral disease and partial pulmonary atelectasis a catheter wedged into a pulmonary artery at the region of the atelectasis revealed a low blood pressure and marked oxygen desaturation, in contrast to a normal wedge pressure and oxygen saturation in the hilar region. There was also a slight reduction of the peripheral arterial oxygen content. These findings are interpreted by the authors on the assumption of a direct communication of a branch of the pulmonary artery and a bronchial vein that came into function in the course of the atelectasis and caused an intrapulmonary right-to-left shunting of blood, circumventing the pulmonary capillaries. Such short cuts in the pulmonary circulation have been described previously by Hayek on the basis of anatomic-histologic studies and were termed "Sperrarterien."

PICK

Hammond, J. D. S.: The Physical Properties of the Lungs in Chronic Cor Pulmonale. Clin. Sc. **16**:481 (Aug.), 1957.

Pulmonary compliance and nonelastic resistance were studied in 5 normal subjects and 31 with chronic bronchitis and emphysema. Twelve of 17 with chronic cor pulmonale were studied during heart failure and 10 were restudied after recovery. Patients with emphysema and especially those with chronic cor pulmonale showed increased inspiratory and expiratory nonelastic resistance compared to normal individuals. Mean compliance was lower in individuals with emphysema than in normal subjects. The compliance was less in every case of congestive failure than the lowest value in emphysema. After recovery from heart failure, pulmonary resistance decreased and compliance increased but largely remained lower than in emphysema alone. Since the only 5 patients whose compliance returned to levels found in uncomplicated emphysema were those who subsequently required neither diuretics nor salt restriction, this value is suggested as a guide to the prognosis in chronic cor pulmonale.

KURLAND

DuBois, A. B., and Marshall, R.: Measurements of Pulmonary Capillary Blood Flow and Gas Exchange Throughout the Respiratory Cycle in Man. J. Clin. Invest. **36**:1566 (Nov.), 1957.

Certain hemodynamic measurements in the literature tend to indicate the possibility of variations in pulmonary blood flow and vascular resistance with the respiratory cycle. These workers report on the use of a "manometric respirometer" for the measurement of absorption of nitrous oxide in normal man. The data led to the conclusion that the exchange of inert, soluble gas between the alveoli and capillaries continues to occur evenly during both inspiration and expiration. It also appears that pulmonary capillary blood flow does not vary, or varies within narrow limits, throughout the respiratory cycle. It is suggested that during inspiration blood flow increases through the right heart, decreases through the left heart, and is essentially unchanged in the pulmonary capillary bed. The reverse of these changes is found during expiration. However during slow inspiration, the blood flow is increased in both right and left heart and the pulmonary capillary bed. Similarly, the flow is decreased in all of the 3 vascular systems during slow expiration.

WAIFE

RENAL AND ELECTROLITE EFFECTS ON THE CIRCULATION

Farber, S. J.: Physiologic Aspects of Glomerulonephritis. J. Chron. Diseases **5**: 87 (Jan.), 1957.

In this article, the author reviews several aspects of renal function and hemodynamics and again indicates the reduced inulin clearance, the low filtration fraction, the altered excretory and resorptive T_m's, the associated electrolyte and water abnormalities and the changes in cardiovascular hemodynamics noted in this disease. Based on this information, the author proposes a scheme of pathogenesis of vascular congestion in acute nephritis.

MAXWELL

Berliner, R. W., and Davidson, D. G.: Production of Hypertonic Urine in the Absence of Pituitary Antidiuretic Hormone. J. Clin. Invest. **36**: 1416 (Oct.), 1957.

The experiment described in this paper was devised to study whether it would be possible to reduce glomerular filtration rate in the absence of antidiuretic hormone (ADH). An inflatable cuff was devised to compress the renal artery in 12 dogs. Inflation of the cuff during maximum water diuresis was accompanied by a depression in glomerular filtration rate and a rise in the concentration of the urine from the experimental kidney. At the same time, in each animal, urine hypertonic to the plasma was obtained from the experimental kidney when the urine from the control kidney was indicative of water diuresis. Thus, it was possible for one kidney to produce urine hypertonic to plasma while the other excreted water at a maximal rate. Participation of ADH could be excluded because normal diuresis was

maintained by the contralateral, or control, kidney. The important factor is believed to be the reduction of glomerular filtration and thus the filtered load of sodium and chloride in each nephron. Since reduced amounts of these electrolytes reach the renal segment responsible for urine dilution, the extent to which the urine can be diluted is limited. The concentrating mechanism, operating essentially without ADH, is able to remove enough water to render urine hypertonic. These studies indicate that a number of possibilities other than simple changes in the level of circulating ADH must be considered when changes in urine concentration and in the rate of elimination of water loads are encountered.

WAIFE

Moyer, J. H., Burgess, J., and Ford, R. V.: Pyribenzamine (Tripelennamine): Effects on Renal Hemodynamics and the Excretion of Water and Electrolytes. Am. Heart J. 54: 643 (Nov.), 1957.

Data from studies of the effect of Pyribenzamine (tripelennamine) on renal hemodynamics and water and electrolyte excretion on a group of laboratory animals and human subjects are presented. In dogs no significant alteration in water and electrolyte excretion could be demonstrated. When given to human subjects with either heart failure or the nephrotic syndrome associated with glomerulonephritis Pyribenzamine did not produce any significant changes in renal function or in water and electrolyte excretion.

SAGALL

Holzmann, M.: ECG and Electrolytes. Cardiologia 31: 209 (Sept.), 1957.

Since action currents, recorded by the electrocardiogram, represent variations of electric potentials produced by ionic shifts, disorders of the distribution of electrolytes and of their balance in body fluids, must of necessity lead to electrocardiographic alterations. The *magnitude* of the resting and action potentials across the membrane of the myocardial cell depends on intracellular and extracellular concentration of potassium and sodium ions, regulated by membrane activity, whereas the *duration* of the state of depolarization is regulated by the calcium concentration. The role of sodium, however, appears to be only a secondary one. Certain conflicting experimental data and the fact that blood electrolyte levels in man cannot always be correlated in a quantitive manner with typical electrocardiographic patterns, suggest that the electrocardiographic manifestations may not depend on the actual blood concentration of a certain electrolye. For potassium this could be explained by changes in the gradient between intracellular and extracellular concentration, which has been established to be 30 under normal conditions. A hypokalemic alteration of the electrocardiogram could, for instance, be the consequence of augmentation of the gradient which could be caused by actual reduction of the blood potassium level as well as by accumulation of potassium ions in the cell interior, in the face of a normal blood potassium. By the same token a reduction of the potassium gradient across the cell membrane will produce a pattern of hyperkalemia, regardless of whether this is due to actual increase of extracellular potassium or a decrease of its intracellular concentration. Similar discrepancies between electrocardiographic manifestations of hypocalcemia and laboratory determination of blood calcium levels could be resolved by consideration and the separation of ionized and protein-bound blood calcium fractions.

PICK

Hegglin, R.: Myocardial Function in Electrolyte Disorders. Cardiologia 31: 195 (Sept.), 1957.

Electrolytes are the most important factor in the regulation of the process of contraction, and hence, an imbalance of ionic concentration is manifested clinically in disturbances of myocardial function and electrocardiographic abnormalities, in particular in the form of a concomitant, or dissociated, alteration of the duration of the mechanical and "electrical" systole, demonstrable by simultaneous recording of the electrocardiogram and the phonocardiogram. The conditions are simplest in various states leading to hypocalcemia in which the Q-T interval is usually prolonged in proportion to the delay of the onset of the second heart sound. Isolated prolongation of the Q-T interval under these circumstances suggests some weakness of myocardial contractility. In hypercalcemic conditions, for instance, with diffuse bone metastases, shortening of Q-T may be seen with a normal mechanical systole. Dissociation in an opposite direction, namely shortening of mechanical and prolongation of electric systole, is observed in cases of progressed hypokalemia, provided that a prolongation of the Q-T interval can be distinguished from a T-U superposition. Associated disturbances of other electrolytes may be responsible for this phenomenon, in particular variations in the chloride level. Attempts to correlate such alterations with changes of the sodium balance, alkali reserve, blood protein composition, and blood pressure have thus far failed. Hemodynamic studies under such circumstances suggest a reduction of cardiac work by about 27 per cent.

PICK

Weidmann, S.: Ionic Flux, Action Potential and Contraction of the Heart Muscle. Cardiologia 31: 186 (Sept.), 1957.

On the basis of experiments with radioactive isotopes on isolated (nerve) fibers, the following concentration gradients across a cell membrane could be established: extracellular/intracellular sodium 10:1, intracellular/extracellular potassium 30:1, and intracellular/extracellular calcium 1:1. Therefore the constant ionic exchange during cellular activity has to take place, at least in part, against a concentration gradient and requires the assumption of some active metabolic mechanism ("sodium pump"). The release of potassium by heart muscle fibers increases with mechanical stress, whereas the absorption of potassium seems to be reduced under the influence of ouabain. Introduction of a microelectrode into the cell interior permits measurements of potential difference of about 90 mV, the membrane resting potential, which is the result of different ionic concentrations at the 2 sides of the cell membrane. Cellular activity is signaled by temporary abolishment of this potential difference corresponding to a sudden change of selective permeability of the membrane. Records of these variations of potential differences associated with cell activity, result in a monophasic curve termed the membrane action potential. The process of depolarization could be definitely correlated with the sudden influx of sodium into the cell, whereas the process of repolarization appeared to be related to a gradual exit of potassium from the cell. The original concentration gradient across the cell membrane was restored during the subsequent rest period.

The upstroke of the action potential precedes the onset of mechanical contraction, and relaxation commences only after completion of the repolarization, but in which manner mechanical and electrical processes are coupled is at present unknown. Some, partly controversial, data in this respect are as follows: acetylcholine and high potassium concentration cause reduction of both the action potential and intensity of contraction; reduction of glucose substantially reduces contractility with negligible effects on the action potential; removal of calcium from the perfusion fluid abolishes contractility, whereas action potentials continue; increase of calcium leads to augmentation of contractility while the action potential diminishes; finally in solutions low in sodium, contractions become more vigorous, whereas the action potential loses in amplitude and duration.

PICK

Fabre, J.: Electrolyte Disturbances in Heart Failure. Cardiologia 31: 219 (Sept.), 1957.

Congestive heart failure is associated with an augmentation of total blood volume without modification of the electrolyte concentration. Among 162 patients, hyponatremia was found in only 12 instances and in each could be explained as a consequence of therapy or on the basis of a complication. Disorders of electrolytes appear if elimination of sodium occurs too suddenly at a time when venous pressure becomes normalized. Difficulties in water excretion, on the other hand, result in sodium retention. Edema in congestive heart failure, is the result of exaggerated tubular salt absorption. This comes into action whenever the circulating blood volume decreases. In cardiac patients with reduced cardiac output, such a salt retention increases the actual blood volume, but, due to venous stasis and edema formation, reduces the effective volume, thus establishing a vicious circle. On the other hand, reduction of renal blood flow by itself probably also influences tubular water and salt reabsorption. The role of aldosterone in the maintenance of homeostasis has not yet been established. In some cardiac patients the blood aldosterone is elevated but in an inconsistent manner.

PICK

RHEUMATIC FEVER

Lazar, H. P., Maas, G. I., Lipscomb, W. R., Hammond, J. H., and Rantz, L. A.: Streptococcal Disease and Rheumatic Fever in Air Force Recruits. I. Epidemiology and Clinical Picture of Acute Rheumatic Fever. Arch Int. Med. 100:604 (Oct.), 1957.

Fifty-eight cases of acute rheumatic fever in Air Force recruits at a northern California basic training center are reported. These occurred within a 6-month period in a normally low-incidence area for this disease. All but 1 case occurred in basic trainees rather than in the permanent base personnel. The epidemiology leading to the outbreak and bacterial evidence of streptococcal carrier states prior to the outbreak were well documented. The symptoms, signs, and laboratory data closely followed the criteria accepted for the diagnosis of acute rheumatic fever. In the epidemic group, evidence of recent streptococcic infection could be inferred in 47 patients or 81 per cent, either by throat cultures or significant antistreptolysin-0 titers. In order to eradicate the streptococci all patients with rheumatic fever were given 250,000 units of oral buffered penicillin G daily for the first 10 days and 250,000 units twice daily for the duration of their hospital stay. In addition, salicylates alone were used in 35 patients, cortisone alone was used in 1 patient and salicylates and cortisone as combined therapy were used in 21 patients. The

authors cite their experiences relative to the clinical course of these patients plus the evidence for residual carditis. On adequate therapy, fever and arthralgia disappeared within a week in approximately 75 per cent of the patients. Although a control group was not available, it was the clinical impression of the authors that in the dosage utilized, steroids did not appreciably alter the course of the patients observed. Despite the apparent mildness of the majority of the cases, the early institution of adequate therapy and a period of hospitalization of at least 3 months, 26 per cent of the group developed valvular disease of a sufficient degree to result in a medical discharge. Since the carrier state may be epidemic for streptococci and this state usually antedates clinical evidence of acute rheumatic fever, the obvious value of the possible elimination of the streptococcic carrier state by the use of penicillin can be concluded. This concept is particularly applicable in regard to the use of penicillin prophylactically in those patients already once afflicted with acute rheumatic fever.

KRAUSE

Lazar, H. P., Maas, G. I., Lipscomb, W. R., Hammond, J. H., and Rantz, L. A.: Streptococcal Disease and Rheumatic Fever in Air Force Recruits. II. Prophylaxis with Tandem Oral Penicillin. Arch. Int. Med. **100**:614 (Oct.), 1957.

It has been documented that when large numbers of recruits are exposed to virulent streptococci, epidemics of acute rheumatic fever with associated carditis may result. In a previous study, the authors described their experience with an epidemic consisting of 58 patients with acute rheumatic fever. A base-wide oral penicillin prophylactic program was instrumental in aborting the tail of the epidemic. Based on these facts, plans were then formulated and set into action to avert a repetition of this experience during the following respiratory disease season. In the current study, an intensive search was made to discover streptococci as the bacteriologic agent in all sore throats occurring in base personnel. In a 5-week period 186 of 581 throat cultures or 32 per cent were found to yield B-hemolytic streptococci, and in this same interval 8 patients with acute rheumatic fever were hospitalized. There then followed a penicillin prophylaxis program of 6 months. During this time, all recruits were given 250,000 units of oral buffered penicillin G twice a day for 10 days. From the inception of the program, in tandem fashion, all recruits upon reaching the fourteenth day of residence upon the base were similarly protected. A total of 25,305 patients were included in this penicillin-protection program. This caused a lowering of the presence of beta-hemolytic streptococci (which sought in the dispensary throat culture program) to less than 5 per cent or approximately one sixth of its initial level. In a 6-month period during which the effects of the penicillin prophylaxis were in force, a total of 7 patients with acute rheumatic fever were encountered. None of these, for various reasons, could actually be classified as penicillin failures. The aim of the project was to protect each man at the time of increased risk of acquisition of the streptococcic carrier state. The authors admit that there are defects in this system of protection, and suggest a trial of tandem intramuscular benzathine penicillin for future study.

KRAUSE

McCue, C. M.: Steroid Therapy for Rheumatic Fever. J. Pediat. **51**:255 (Sept.), 1957.

This is a report of a series of 94 patients treated with cortisone over a prolonged period of time after the initial attack of rheumatic fever. The drug dosages varied, but some attempt was made to divide the total number of patients into 4 fairly evenly distributed groups, depending upon the daily amount of cortisone. The individuals selected for inclusion in the study were acutely ill patients and, therefore, the study was somewhat biased. There were 8 deaths. As a result of this study, the investigators recommend 300 mg. of cortisone be given daily for 21 days with tapering after that. The statement was made that of the number of patients included in the study, 36 had heart disease at the onset of therapy, and of these 36, 14 have no heart disease at the present time (by the same investigators' followup in one year.) This was compared to a series of cases followed before 1948, in which 132 patients with heart disease seen during a first attack were subsequently examined. One-hundred and nine had heart disease at the end of 3 years of observation. The authors concluded that the residual heart damage was cut by 50 per cent by such steroid therapy given over the time period and the dosage range cited above.

HARVEY

Lessof, M., and Brigden, W.: Systolic Murmurs in Healthy Children and in Children with Rheumatic Fever. Lancet **2**:673 (Oct. 5), 1957.

One hundred healthy children and 200 children with rheumatic fever were examined to reassess the incidence and character of systolic murmurs. Short, usually soft, systolic murmurs were found in more than 90 per cent of healthy children. In the presence of chest deformity, they may be moderately loud. A systolic murmur was heard in all patients with rheumatic fever. Organic mu-

murs were present in 67 of 100 patients suffering their first attack; 36 of these were apical pansystolic murmurs. Of those patients who had suffered more than 1 attack of rheumatic fever, 64 had an apical pansystolic murmur and 27 others had diastolic murmurs. The diagnosis of rheumatic valvulitis must depend on the finding of a pansystolic murmur or a diastolic murmur. The length of an organic murmur in rheumatic fever is its principal distinguishing feature. Soft midsystolic murmurs are almost certainly innocent.

KURLAND

Illingworth, R. S., Jowett, G. H., and Gibson, W. M.: Cortisone Treatment of Rheumatic Fever. Relationship of Weight to the Speed of Fall of Erythrocyte-Sedimentation Rate. Lancet 2:659 (Oct. 5), 1957.

The rate of fall of the sedimentation rate in 18 overweight children with rheumatic fever receiving cortisone with or without salicylates was significantly slower than in 30 underweight children. There was no corresponding difference in the rate of fall of the sedimentation rate in 75 children receiving salicylates alone. It is suggested that this is evidence for different modes of action of these therapies.

KURLAND

Illingworth, R. S., Lorber, J., Holt, K. S., Rendle-Short, J., Jowett, G. H., and Gibson, W. M.: Acute Rheumatic Fever in Children. A Comparison of Six Forms of Treatment in 200 Cases. Lancet 2:653 (Oct. 5), 1957.

The results are presented of 9 years' experience with 6 different forms of treatment used in 200 patients with rheumatic fever. Cortisone with salicylates in high dosage caused a more rapid fall of the sedimentation rate than any other treatment. Cortisone with or without salicylates was more effective than salicylates alone and salicylates were more effective than no specific treatment. The duration of arthritis and of fever was less in the cortisone group than in the salicylate group and less in the latter than in the "no-treatment" group. New rheumatic manifestations did not develop during cortisone treatment. The course of carditis with respect to loss of organic systolic or diastolic murmurs was more favorable in the cortisone cases. Therapy of carditis was most effective when initiated within 30 days after the onset of rheumatic fever.

KURLAND

ROENTGENOLOGY

Schmidt, J.: Roentgen Diagnosis of the Lusoric Artery. Fortschr. Rontgenstr. 86: 188 (Feb.), 1957.

The lusoric artery is a variant of the right subclavian artery that occurs with a frequency of less than 1 per cent. It originates as the most distal large vessel on the aortic arch and has to cross the esophagus, usually behind, in order to reach the right side. The author presents radiographs of this anomaly as it occurred in several patients. On the plain chest film the aortic knob was unusually prominent, and the barium filled esophagus showed a distinct impression either anteriorly or posteriorly at the site of the crossing. The artery could actually be seen as a thin band coursing obliquely and to the right in the area of the esophageal impression. It is pointed out that an abnormally prominent aortic knob especially in young women or children should make one suspicious as to the presence of this aberrant blood vessel. The author discusses other methods of proving the presence of this and other rarer variants of the large vessels originating from the aortic arch. Among them are angiography, catheterization, and exertion of pressure through the esophagus leading to disappearance of the pulse in the affected vessel.

SCHWEDEL

Michel, D., Herbst, M., and Bock, K.: Angiocardiographic Aspects of the Bernheim Syndrome. Fortschr. Rontgenstr. 86: 181 (Feb.), 1957.

In 1910 Bernheim reported that hypertrophy of the left ventricle led to the clinical picture of isolated right ventricular failure. Presumably the interventricular septum hypertrophied to such an extent that it encroached on the cavity of the right ventricle and led to a hemodynamic situation similar to that of tricuspid stenosis, without having given rise at first to the syndrome usually associated with failure of the left ventricle. A survey of the literature indicates that there are valid arguments based on anatomical, clinicopathologic and physiologic grounds that militate against accepting this syndrome as a true entity. Angiocardiograms of 2 children with congenital aortic stenosis are presented. Both of these reveal peculiar indentations of the interventricular septum into the cavity of the right ventricle. The author points out that this finding is a rarity, as it occurred only twice in 300 angiocardiographic examinations in normal individuals and in patients with congenital or acquired heart disease. It is noteworthy that the 2 patients described did not satisfy the criteria of the Bernheim syndrome, since only 1 of them had left ventricular hypertrophy, and neither of the patients developed right ventricular failure. It is implied that the abnormality reported need not produce the hemodynamic sequence postulated for

the Bernheim syndrome. Thus, the author, like others before him, is skeptical as to the occurrence of this condition.

SCHWEDEL

Ziegler, G.: Pre- and Postoperative Angiography in Cases of Peripheral Vascular Injury. Fortschr. Rontgenstr. **86**: 172 (Feb.), 1957.

Arteriography was performed before and after operation for traumatic arterial aneurysm just below the knee in 1 patient; and in another patient with an upper tibial arteriovenous aneurysm. A manual cassette changer was employed. Injection was made proximal to the damaged sites, and the author believes this is better than direct injection into the aneurysm. Proximal to the lesion tortuosity of the femoral artery was seen in the case of an arterial aneurysm but not in that of the arteriovenous aneurysm. In terms of hemodynamics this is explained by an increased resistance to flow with the arterial aneurysm, and to decreased resistance in the arteriovenous variety. Injury to the wall of the veins in the path of blood with arterial flow and pressure characteristics are described as the cause for the abnormal venogram in the case of the arteriovenous aneurysm.

SCHWEDEL

Gumrich, H., Dortenmann, S., and Kubler, E.: Diagnosis of Arterial Changes Induced by Local Factors. Fortschr. Rontgenstr. **86**: 162 (Feb.), 1957.

This is a report of a series of cases in which localized arterial damage had occurred. The patients were studied by the usual clinical procedure, soft tissue x-rays, oscillometry, oscillometry after application of tourniquets and serial angiography by aortography or arteriography. The authors classify these cases into 6 etiologic categories: blunt trauma, fractures, gun shot wounds, inflammatory and scarring processes, frostbite, and circumscribed functional changes such as those following arterial puncture. The following pathogenetic processes occur in the different groups: thrombosis, rupture, arterial or arteriovenous aneurysms, intimal reactions with secondary arteriosclerosis, and local spasm. Volkman's contracture and Sudeck's atrophy are mentioned as special complications of locally induced arterial damage. Presumably, a relative slowing of the blood stream is characteristic for the limb affected by the latter condition. Stress is placed on the history or presence of local disease or injury in the differential diagnosis of these conditions from vascular disturbances caused by systemic or neurologic disease or dysfunction.

SCHWEDEL

Hasse, H. M., and Dembowski, U.: Angiography of Arterial Occlusions and Their Collateral Circulation in the Lower Extremities. Fortschr Rontgenstr. **86**: 153 (Feb.), 1957.

The authors describe in a systematic fashion the effects of occlusions of individual arteries in the lower extremities as illustrated by angiography. They point out that in peripheral arterial disease multiple vascular involvement is the rule. Localization and extent of the occlusions determine the character of the collateral circulation. Collateral vessels develop most often from anatomically known anastomoses. In isolated instances, however, as with segmental occlusions, bridge anastomoses are formed with direct connections between vascular stumps. Retrograde arteriography through the femoral artery is at times more effective than aortography for the demonstration of arterial occlusions in the pelvis.

SCHWEDEL

Volpel, W.: Arteriography of Arterial Spasm Fortschr. Rontgenstr. **86**: 79 (Jan.), 1957.

Even though spasm of larger arteries is known to occur, it has only rarely been demonstrated by arteriography. The author, therefore, has selected 6 cases out of 500 arteriograms where he was able to document, by control studies, that narrowing of the lumen of larger arteries was due to spasm. Thus, there are reproduced paired arteriograms that show specific arteries with and without spasm. It is stressed that from the radiologic standpoint it is impossible to tell spastic from organic arterial occlusions except in the presence of control arteriograms.

SCHWEDEL

Burgemeister, G., Westerkamp, H., and Feller, H.: Angiocardiography in Congenital Heart Disease. Fortschr. Rontgenstr. **86**: 25 (Jan.), 1957.

The authors report their 4-year experience in 550 cases studied by angiocardiography. Depending on the suspected nature of the problem they use the intravenous route, selective angiocardiography, or retrograde aortography. Indirect (venous) angiocardiography is recorded either by serial exposures of the fluoroscopic image on 70 mm. film (up to 6 exposures per second), or by cinefluorography (16 to 50 exposures on 35 mm. film). Stereoscopic effects may be obtained by the use of a pendulum apparatus inducing rotation of the target surface. Venous angiocardiography is employed in patients with venoarterial shunts (Fallot, truncus, tricuspid stenosis, Ebstein, Eisenmenger, transposition, Taussig-Bing); selective angiocardiography for septal defects, pulmonary arteriovenous fistula, pulmonic stenosis; retrograde aortography for patent ductus

arteriosus, aortopulmonary defects. The authors advise against the use of angiocardiography immediately following cardiac catheterization. Excellent illustrations are offered of characteristic lesions in Fallot, tricuspid stenosis, Ebstein's anomaly, patent ductus, and aortic coaretation.

SCHWEDEL

Smith, R. C., Goldberg, H., and Bailey, C. P.: Pseudoaneurysm of the Left Ventricle: Diagnosis by Direct Cardioangiography. Report of Two Cases Successfully Repaired. Surgery 42: 496 (Sept.), 1957.

Pseudoaneurysm in this paper refers to a false aneurysmal sac in which the walls are formed by pericardium or other adjacent extracardiac tissue and the interior communicates with the ventricular lumen through the site of the previous cardiotomy incision. Both patients were women in their thirties who had had prior operative procedures on the left ventricle. In 1 instance the left ventricle had been perforated accidentally and repaired during a mitral commissurotomy procedure. The other patient had undergone simultaneous, combined surgery for aortic and mitral stenosis with the aortic valve being approached by the transventricular route. Chest roentgenograms in each instance disclosed an abnormal, bulging shadow along the left cardiac border. Direct cardioangiography via the transthoracic approach to the left atrium provided, in each instance, clear and conclusive evidence that the abnormal bulge was directly connected with the left ventricle and filled from it. Surgical repair of the abnormal communication between the ventricle and the false aneurysm was effected by fingertip tamponade of the opening and then passing mattress sutures beneath the tamponading finger. The aneurysmal sac was then removed. Each patient made a good recovery. The authors are of the opinion that ventricular defects of the nature described in this report are likely to increase as advances in cardiac surgery are made and technics are developed that employ an increasing number of ventricular incisions. The effectiveness of direct angiocardiography in the differential diagnosis of these lesions is emphasized. Details of the technics of direct angiocardiography and of the surgical procedure employed are presented.

BROTHERS

Radke, H.: Arteriography of Local Vascular Changes in the Foot. Fortschr. Rontgenstr. 86: 177 (Feb.), 1957.

Vascular impairment in the foot as a result of external injury is both organic and functional in character. The author maintains that the presence of reversible symptoms and the appearance of spastic changes on the arteriogram point to autonomic nervous system imbalance of the peripheral vessels in the affected patients pre-existent to the injury. To illustrate this thesis angiograms of the feet of patients who had previously sustained amputations for frostbite are presented. The author uses serial arteriography in 2 planes in order to localize the vascular damage and to arrive at an estimate of hemodynamic relationships.

SCHWEDEL

SURGERY AND CARDIOVASCULAR DISEASE

Mounsey, P.: Determination of Success after Mitral Valvotomy. Role of Circulatory Obstruction of the Myocardium and of Other Factors. Brit. M. J. 2: 311 (Aug. 10), 1957.

The authors report on the progress of 169 patients during a 2- to 6-year period after mitral valvotomy. An attempt was made to assess the relative importance of various factors in determining clinical improvement in the long-term follow-up period. A successful result in this time period was related primarily to the degree of surgical success in removing obstruction of blood flow through the mitral valve. Enlargement and failure of the right heart, associated extensive calcification of the mitral valve, associated aortic stenosis, intercurrent emphysema, and recurrent bronchitis adversely affected the results of surgical treatment, while associated mitral or aortic incompetence, and the presence of pulmonary hypertension prior to surgery did not appear to detract from improvement after operation.

SAGALL

Kroboth, F. J., Jr., Barnes, W. H., and Ellis, F. H., Jr.: The Effect of Cortisone on the Healing of Aortic Homografts. An Experimental Study. Surgery 42: 347 (Aug.), 1957.

This study was undertaken to determine whether or not the strength as well as the gross and microscopic evidence of the healing of aortic homografts in dogs was affected by the administration of cortisone. In 46 adult mongrel dogs the segment of abdominal aorta extending from just below the renal arteries to just above the bifurcation was replaced with a homograft obtained from donor dogs and stored for not longer than 6 weeks. The strength of the aorta was tested 14 days after placement of the graft in 34 dogs and 7 days after placement in 12. The dogs were further divided into 7 groups with 2 groups serving as controls and the other 5 groups given different amounts of cortisone over a varying period of days prior to operation. Seven or 14 days after operation the dogs were killed with pentobarbital

sodium and the strength of the grafted segment was tested in situ with blood under pressure. The pressure was increased 100 mm. Hg each minute until a pressure of 700 mm. Hg was reached or until a leak occurred. Fifteen of the original 46 animals were not tested for various reasons. In the group of dogs tested 14 days after operation the results did not show a significant difference between healing of the homograft in the control groups and in those dogs that received varying doses of cortisone. In the dogs tested 7 days after operation the results in the control animals and in those treated with cortisone were practically identical. At the conclusion of each test, the homograft was removed and opened and examined for thrombosis. A greater incidence of complete occlusion and moderate grade of thrombosis was apparent in the animals that had received cortisone. Microscopic examination of sections taken across the lines of anastomosis and stained with hematoxylin and eosin and elastic tissue stains failed to disclose a significant difference in healing of the homografts in the control groups and in the cortisone-treated groups. The abdominal wounds of the dogs that received cortisone did not appear to heal as well as did the wounds in the control animals.

BROTHERS

Rosenberg, J. C., Emerson, E. C., and Murphy, T. O.: A Clinical study of Embolectomy. Angiology **8**: 371 (Oct.), 1957.

Prior to 1950 the authors obtained favorable results from embolectomy in 2 of 14 patients. Subsequently, using a revised approach, 49 of 63 embolectomies were successful. This approach includes operating promptly, usually under local anesthesia; the intra-arterial injection of papaverine (30 mg.) and heparin (10 mg.) when the embolus lies in the femoral system; periarterial sympathectomy; the requirement of adequate bleeding from all vessels opening into the arterial incision after removal of the embolus; postoperative heparinization in instances of iliac or femoral emboli; and whole body heating to 85-90°. All emboli in the latter series were thought to arise from the heart. Forty-three of these patients had atrial fibrillation, 10 had acute myocardial infarction, and 10 had other cardiac lesions. The embolus lodged at the aortic bifurcation in 9, in the iliac arteries in 18, at the division of the common femoral arteries in 38, and in the axillary or brachial arteries in 4. Emboli in smaller arteries are best treated medically. In no instance was a viable limb preserved after unsuccessful embolectomy, and 16 patients died following surgery.

ROGERS

VALVULAR HEART DISEASE

Soulie, P., Joly, F., Carlotti, J., and Servelle, M.: Recurrence of Tight Mitral Stenosis Syndrome After Commissurotomy. Am. Heart J. **54**: 695 (Nov.), 1957.

In a series of 380 mitral commissurotomies performed during the period from 1950 to 1956, the authors found 6 patients in whom a syndrome of tight mitral stenosis occurred from 9 months up to 3 years after operation. A second surgical procedure was performed in these patients and the diagnosis confirmed. To this group were added 5 similar patients already published by various authors. The recurrence of mitral stenosis after commissurotomy was found to be rare. Almost every instance was observed in young patients under the age of 30. In most of the patients, the cause seemed to be a refusion of the mitral commissures. Recurrence of tight mitral stenosis was noticed only in patients who had had an incomplete commissurotomy, that is, no instrumental dilatation and incomplete fracture of both commissures. The recurrence of the stenosis was marked by symptoms due to an increase of the lesser circulatory pressure, frequently appearing abruptly 1 to 3 years after a regression of the original symptoms after operation. This study points out the improved value of fracture of the valves by instrument and the possible help and usefulness of an anti-inflammatory and anticoagulant treatment during the postcommissurotomy period.

SAGALL

Bayer, O., Grosse-Brockhoff, F., Loogen, F., and Meessen, H.: Comparative Clinical, Pathophysiologic and Anatomic Studies in Mitral Stenosis. Arch. Kreislaufforsch. **26**: 238 (June), 1957.

In 200 pulmonary biopsies obtained during commissurotomy in mitral stenosis, the histologic changes in the pulmonary arteries and other pulmonary structural elements show an almost perfect correlation with the degree of pulmonary hypertension measured by means of cardiac catheterization. This makes it unnecessary to assume active constriction of the pulmonary blood vessels as the cause of pulmonary hypertension, which can be explained entirely on an anatomic basis. The degree of pulmonary changes was also parallel to the degree of cyanosis, prominence of the pulmonary conus, intensity of the vascular pattern and the electrocardiographic signs of right ventricular hypertrophy. The latter were absent if the mean pulmonary artery pressure was less than 60 mm., but were always present if it exceeded 90 mm.

LEPESCHKIN

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3 NEW CAREER INVESTIGATORS NAMED BY HEART ASSOCIATION

The Association has appointed three new Career Investigators, bringing to six the number of scientists whose research is being supported on a lifetime basis by the Association and its affiliates. The latest appointments include two faculty members of Columbia University College of Physicians and Surgeons, David B. Sprinson, Ph.D., Professor of Biochemistry, and John V. Taggart, M.D., Professor of Medicine, and Lewis W. Wannamaker, M.D., Associate Professor of Pediatrics, University of Minnesota Medical School.

Already working as Career Investigators are Victor Lorber, M.D., University of Minnesota, appointed in 1951, and John R. Pappenheimer, Ph.D., and Albert H. Coons, M.D., both of Harvard Medical School and both named in 1953.

Dr. Sprinson

Dr. Sprinson, 48, is working in the general field of intermediary metabolism. In some 15 years of research at Columbia University, he has studied a number of complex aspects of the body's use of amino acids for the formation of proteins, nucleic acids and certain types of fatty materials, such as phospholipids. Dr. Sprinson has also worked on the origin of the benzene ring in nature.

The first Established Investigator of the Heart Association to be advanced to Career Investigator, Dr. Sprinson received both his undergraduate and graduate training in New York City. He received his B.S. degree at the College of the City of New York in 1931, his Master's degree at New York University in 1936, and his Ph.D. at Columbia University in 1946. He was Assistant in Biochemistry at Montefiore Hospital, Laboratory Division, from 1931-41. Dr. Sprinson joined the research staff of the Department of Biochemistry at Columbia in 1942, becoming

CAREER INVESTIGATOR PROGRAM

The Career Investigatorship program of the Association dates back to its early days as a national voluntary health agency. Reorganized in 1948 after 24 years as a small medical and professional society, the Association gave first priority in its new program to the encouragement and support of medical research. It adopted the policy of allocating at least half the income received by its National Office to support of research, and it determined that in awarding these funds, chief emphasis would be placed on the long-term support of *individuals*, rather than projects.

The Career Investigatorship—allowing a lifetime for scientists of proved capacity to pursue their ideas without restriction, wherever they may lead—is the highest expression of this concept. Providing $30,000 annually to cover salary and help underwrite the recipient's laboratory expenses, it relieves him of pressures arising from short-term forms of support or the need to supplement his income through teaching or other non-research activity.

Applications for Career Investigatorships *are not accepted.* Nominations by deans of medical schools, heads of departments or similar eminent individuals are welcomed in letter form indicating the qualifications of the nominee. All former AHA Established Investigators will automatically be considered as candidates for Career Investigatorships. Appointments in this category will be made at irregular intervals. A brochure regarding nomination procedures may be obtained from the Assistant Medical Director for Research, American Heart Association, 44 East 23rd Street, New York 10, N.Y.

successively Research Associate, Assistant Professor, Associate Professor of Biochemistry and Professor of Biochemistry. During 1952, Dr. Sprinson held a Fulbright scholarship to the University of Paris and was a Guggenheim Fellow in 1957.

Dr. Taggart

Dr. Taggart, 41, is a physiologist and biochemist whose chief sphere of interest is the mechanisms of renal tubular transport, and especially with active transport against concentration gradients. With R. J. Cross, he developed a method for the study of transport in kidney slices which has permitted the rapid accumulation of knowledge concerning the enzyme processes involved.

Dr. Taggart was educated at the University of California and the University of Southern California, receiving his M.D. degree at the latter in 1940. His postgraduate training included an internship at the Los Angeles County General Hospital, assistant residency at the University of Chicago Clinics and research fellowship training at Goldwater Memorial Hospital, New York. In 1946 he joined the Department of Medicine at Columbia University as a Welch Fellow in Internal Medicine of the National Research Council. He became Associate Professor of Medicine in 1954 and Professor of Medicine in 1958. In 1952, Dr. Taggart was awarded the Edward N. Gibbs Memorial Prize by the New York Academy of Medicine for his studies in renal physiology.

Dr. Wannamaker

Dr. Wannamaker's present research is concerned primarily with enzymes produced by various strains of group A hemolytic streptococci. He is well known for his contributions to the epidemiology of streptococcal infection through the studies he helped design and conduct while serving with the Streptococcal Disease Laboratory at Warren Air Force Base in Wyoming from 1948-52.

Dr. Wannamaker, 35, received his undergraduate training at Emory University, Atlanta, and in 1946 took his M.D. degree at Duke University Medical School, Chapel Hill, N.C., where he later interned in pediatries. This was followed by an assistant residency at Willard Parker Hospital for Contagious Diseases in New York. In 1953 Dr. Wannamaker joined the staff of the Department of Pediatries, University of Minnesota. He was promoted to Assistant Professor of Pediatries in 1954, and to Associate Professor in 1955. On a leave of absence from the University in 1955, Dr. Wannamaker served as Visiting Investigator at the Rockefeller Institute laboratory of Dr. Maclyn McCarty, past-chairman of the Heart Association's Council on Rheumatic Fever and Congenital Heart Disease. As a member of the Council's Committee on Prevention, Dr. Wannamaker participated in the preparation of its "Statement on the Prevention of Rheumatic Fever and Bacterial Endocarditis."

The awards to the new Career Investigators were effective July 1, 1958.

APPLICATIONS FOR AHA RESEARCH SUPPORT NOW BEING INVITED

Applications by research investigators for support of projects to be developed during the fiscal year beginning July 1, 1959 are now being accepted by the Association.

The deadline for research fellowship applications and established investigatorships is September 15, 1958. Applications for grants-in-aid must be made by November 1, 1958.

Applications may be made for awards in the following categories:

Established Investigatorships: Awarded for periods of up to five years, subject to annual review, in amounts ranging from $6,500 to $8,500 yearly plus dependency allowance, to scientists of proven ability who have developed in their research careers to the point where they are independent investigators. In addition, a grant of $500 is made to the investigator's department to assist in defraying the expenses of his research program. Applicants for Established Investigatorships may apply for grants-in-aid to support their research at the same time they apply for Established Investigatorships.

Advanced Research Fellowships: Awarded for periods of one or two years to post-doctoral applicants who have had some research training and experience but who are not clearly qualified to conduct their own independent research. During the second year of tenure they will be permitted to spend up to 25 per cent of their time in professional and scientific activities not strictly of a research nature, providing that these will contribute to their professional development and do not involve services for a fee. These stipends range from $4,600 to $6,500 annually. Additionally, a grant of $500 is made to the investigator's department as in the case of Established Investigatorships.

Research Fellowships: A limited number of awards are available to young men and women with doctoral degrees for periods of one or two years to enable them to train as investigators under experienced supervision. Annual stipends range from $3,800 to $5,700. However, this type of award is primarily made by local Heart Associations.

Grants-in-Aid: Made to experienced investigators to help underwrite the costs of specified projects, such as equipment, technical assistance and supplies.

At least half of all funds received by the American Heart Association's National Office are allocated to research. Almost $31,500,000 has been allocated for research support by the Association and its state and local affiliates and chapters in the past 10 years.

Further information and application forms may be obtained from the Assistant Medical Director for Research, American Heart Association, 44 East 23rd Street, New York 10, N. Y.

AHA SCIENTIFIC SESSIONS OFFER VARIED PROGRAM

Joint participation in the Annual Scientific Sessions of the American Heart Association in San Francisco, October 24-26, by the American Society for the Study of Arteriosclerosis and the Microcirculatory Conference will provide additional interest to the program to be presented this year.

Because of its success last year, an all-day Session for Clinicians will be held concurrently on Friday, October 24, under sponsorship of the Council on Clinical Cardiology. It is expected that many practicing physicians from the Pacific coast and Rocky Mountain areas will be attracted to this session which is a presentation of clinical problems in cardiovascular disease and has been classified by the American Academy of General Practice as acceptable for credit for Academy members.

Following is a tentative schedule of the program:

Friday, October 24

The Scientific Sessions, to be held at the Civic Center, begin Friday morning. A session on genetics will be presented jointly by the Heart Association and the American Society for the Study of Arteriosclerosis. The Society is holding its Annual Meeting to coincide with the AHA Scientific Sessions this year for the first time. Sessions of general interest to physicians will also be held Friday morning under sponsorship of the AHA Councils on Circulation and on Cardiovascular Surgery.

A session sponsored by the Council on Rheumatic Fever and Congenital Heart Disease will be held Friday afternoon, as will a symposium conducted jointly by the Association's Council on Circulation and the Microcirculatory Conference. Friday evening's session will be on the subject of "Instrumental Study of the Heart and Circulation."

Saturday, October 25

Scheduled for Saturday morning are a session on Applied Cardiovascular Research; the Lewis A. Conner Memorial Lecture by John H. Gibbon, Jr., M.D., Professor of Surgery, Jefferson Medical College, Philadelphia, on "Maintenance of Cardio-Respiratory Functions by Extracorporeal Circulation;" the George E. Brown Memorial Lecture by Lewis Thomas, M.D., Professor and Chairman, Department of Pathology, New York University College of Medicine, on the

"Role of Hypersensitivity in Cardiovascular Disease;" and the presentation of the Albert Lasker Award of the American Heart Association for distinguished achievement in cardiovascular research.

On Saturday afternoon, joint Panels on "Emotional and Endocrine Aspects of Cardiovascular Disease" and "Effects of Hemodynamics and Vascular Injury" will be presented in conjunction with the American Society for the Study of Arteriosclerosis.

Sunday, October 26

The schedule for Sunday morning includes simultaneous sessions to be conducted by the Councils on Clinical Cardiology, High Blood Pressure Research, and Basic Science. A special program arranged by the Council on Community Service and Education, "Rewards of Research," designed to interest laymen as well as physicians, will be held Sunday afternoon, as will a program on "Prevention of Rheumatic Fever." The Association's Annual Dinner is scheduled for Sunday evening.

In addition, the program will include the daily showing of a medical motion picture program. Also, a section of scientific and industrial exhibits will be provided. Plans are under way to present awards for the outstanding scientific exhibits on display.

Early Registration Urged

As an inducement to early registration for attending the Scientific Sessions all physicians who register prior to the sessions will receive for the first time this year an advance complimentary copy of the program booklet containing abstracts of the proceedings. At the meeting, these programs will be sold for $1.00. Registration and hotel accommodation forms are now available from the Association.

The Annual Meeting of the Assembly to review national policies and activities of the Association will be held on Monday, October 27 and Tuesday, October 28 at the Hotel Fairmont. The Assembly convenes on Monday morning to hear a keynote address by William P. Shepard, M.D., 2nd Vice President, Health and Welfare Division, Metropolitan Life Insurance Company.

Six Assembly Panels will be in session on Monday. They will discuss the following subjects: Research; Fund Raising and Public Relations; Relationships and Responsibilities Between National, State and Local Heart Associations; Community Service-Screening and Case Finding Programs; The Physician's Continuous Self-Education; and Membership.

The general session of the Assembly meets on Tuesday morning to review Panel recommendations and elect officers and Board members of the Association.

LOW-COST ACCOMMODATIONS FOR WORLD CARDIOLOGY CONGRESS

Arrangements have been made by the Organizing Committee of the Third World Congress of Cardiology for residents, research fellows and young physicians who attend on limited budgets to be accommodated at the Ville Universitaire de Louvain at approximately $2.00 nightly including continental breakfast. Transportation facilities to and from Brussels, about 20 miles distant, will be provided.

Such accommodations may be arranged by writing to Dr. Fr. van Dooren, Secretary of the Congress, 80 rue Mercelis, Brussels. A check representing the total sum for the number of nights anticipated should be included. Checks should be made payable to: Third World Congress of Cardiology, account No. 90.490 at the Banque de la Société Générale de Belgique, 3 Montagne du Parc, Bruxelles (Belgique).

NEW AHA MATERIALS AVAILABLE TO PHYSICIANS

Materials recently issued by the Heart Association which are available to physicians include a statistical handbook on cardiovascular diseases in the U.S., a catalog of current audio-visual materials, a booklet for use with cardiac farmers, and an identification card for patients on long-term anticoagulant therapy.

The new handbook, *"Cardiovascular Diseases in the U. S.—Facts and Figures,"* answers some of the more common questions asked about heart disease statistics. Published by the Heart Association in cooperation with the National Heart Institute and the Heart Disease Control Program of the Public Health Service, the 12-page booklet concerns itself with mortality figures available from the National Office of Vital Statistics, the Bureau of Census and the World Health Organization.

A revised 1958 edition of the Association's *Catalog* lists current films, filmstrips, slides and transcriptions on cardiovascular diseases which are available from Heart Associations and other sources.

Designed to help the farmer and his physician plan together a work "prescription" that is within the patient's capacity, the Association's new booklet, *"A Safe Work Load for Farmers With Heart Disease,"* is based on a series of studies conducted since 1954 at the Agricultural Experiment Station, Purdue University, Lafayette, Ind., and at a number of nearby farms. The 12-page booklet classifies many common jobs on the farm according to the amounts of energy they demand, grouping them into light, moderate and heavy work categories. The research has been supported by AHA, Indiana Heart Foundation, Indiana State Board of Health, and Purdue University.

As a result of requests from a number of Heart Associations and from individual patients on anticoagulant therapy in case of accident, dental surgery or other treatment that may induce bleeding, the Association has developed an *Anticoagulant Identification Card* to be carried by patients. Approved by the AHA Committee on Prothrombin Determinations, the card allows space for the patient's physician to indicate the kind and amount of anticoagulant prescribed.

All of the above materials are available free from local Heart Associations or from the American Heart Association, 44 East 23rd Street, New York 10, N. Y.

MEDICAL BIBLIOGRAPHY ISSUED

The Department of Health, Education, and Welfare of the U. S. Public Health Service has announced publication of the third annual volume of the Bibliography of Medical Reviews. The volume, which contains approximately 2,900 references to articles in clinical and experimental medicine and allied fields in the current journals received by the National Library of Medicine, is available from the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at a price presently estimated at $1.25.

FUND OFFERS FELLOWSHIPS, GRANTS

The Life Insurance Medical Research Fund is receiving applications for awards effective July 1, 1959, as follows: (1) Until October 15, for post-doctoral research fellowships. Candidates may apply for support in any medical science field. Preference is given those interested in fundamental problems, especially as related to cardiovascular function or disease. Minimum stipend is $3,800, with allowance for dependents and travel. (2) Until November 1, for grants to institutions in aid of cardiovascular research. Support is available for physiological, biochemical and other basic work and clinical research in the cardiovascular field. For information and application forms, write to the Fund's Scientific Director, 345 East 46th Street, New York 17, N. Y.

MEETINGS CALENDAR

August 11-14: National Medical Association, Milwaukee, John T. Givens, 1108 Church Street, Norfolk 10, Va.

August 24-29: Congress of Physical Medicine and Rehabilitation, Philadelphia. Frances Baker, 1 Tilton Street, San Mateo, Calif.

October 6-10: American College of Surgeons, Chicago. Michael L. Mason, 40 E. Erie Street, Chicago 11, Ill.

October 13-15: Association of American Medical Colleges, Swampscott, Mass. Mrs. Lotus R. Barnes, 2530 Ridge Avenue, Evanston, Ill.

October 20-23: American Academy of Pediatrics, Chicago. E. H. Christopherson, 1801 Hinman Avenue, Evanston, Ill.

October 24-28: American Heart Association Annual Meeting and Scientific Sessions, San Francisco. American Heart Association, 44 East 23rd Street, New York 10, N. Y.

October 27-31: American Public Health Association, St. Louis. Berwyn F. Mattison, 1790 Broadway, New York 19, N. Y.

October 31-Nov. 1: Central Society for Clinical Research, Chicago. A. S. Weisburger, 2065 Adelbert Road, Cleveland 6, Ohio.

November 6-8: Gerontological Society, Inc., 11th Annual Scientific Meeting, Philadelphia. Joseph T. Freeman, 1530 Locust Street, Philadelphia 2, Pa.

November 14-15: First Annual Symposium on Cinefluorography, Strong Memorial Hospital, Rochester, N. Y. George H. Ramsey, Department of Radiology, Strong Memorial Hospital, Rochester 20, N. Y.

ABROAD

August 15-20: World Medical Association, Copenhagen, Denmark, Louis H. Bauer, 10 Columbus Circle, New York 19, N. Y.

September 14-21: Third World Congress of Cardiology, Brussels. Dr. F. Van Dooren, 80 Rue Mercelis, Brussels, Belgium.

September 22-28: 16th International Congress of History of Medicine, Montpellier, France. Louis Dulieu, Montpellier, (Herault) France.

September 25-28: Third International Congress of Angiology, Venice, Italy. M. Comel, Dermatological Clinic, University of Pisa, Pisa, Italy.

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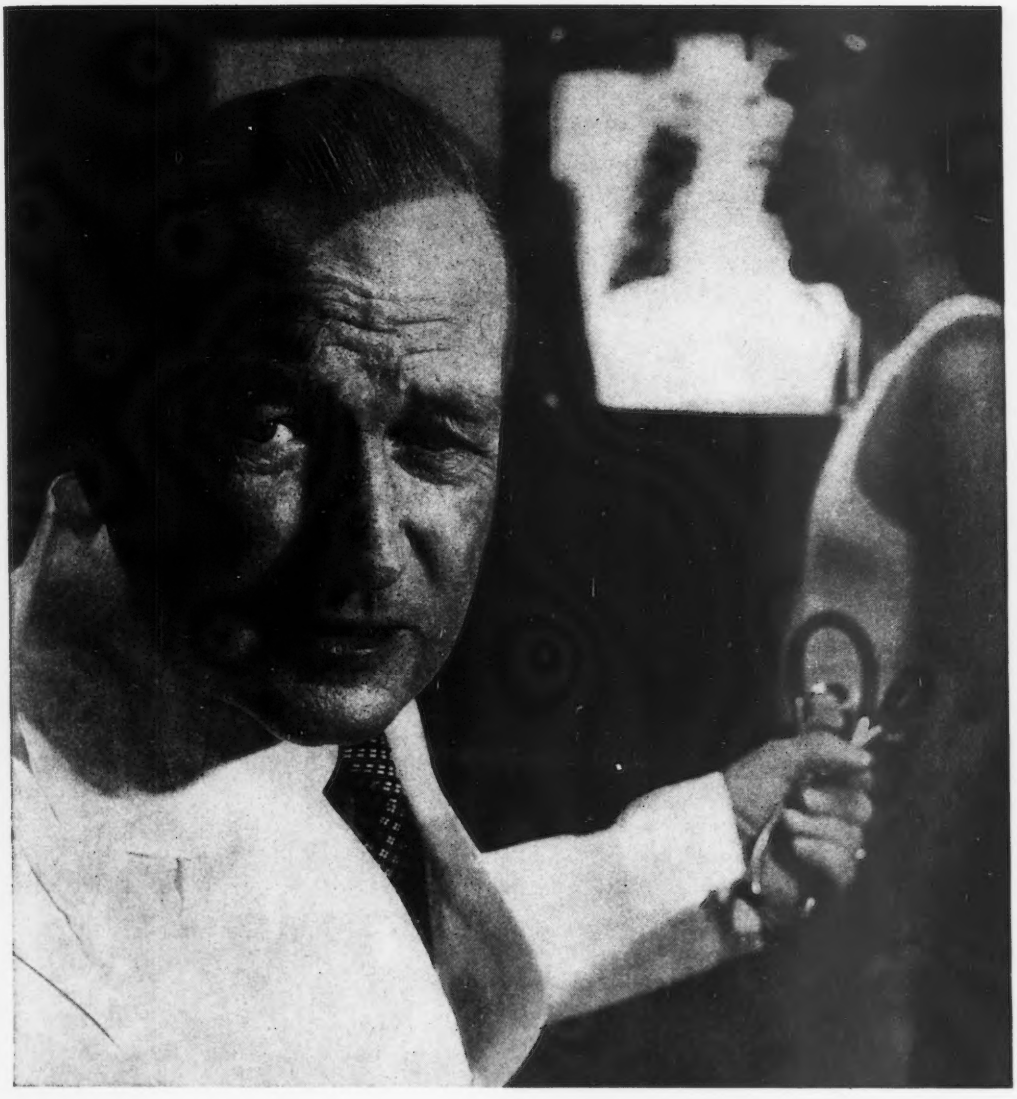

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